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The figure consists of two parts, (a) and (b), each showing a mapping from a 1D sequence to a 2D grid.

Part (a) shows a 1D sequence of 10 elements (represented by squares) being mapped to a 2D grid of 10 rows and 10 columns. The mapping is shown by a sequence of arrows pointing from the 1D elements to the 2D grid. The 1D sequence is:  $\square, \square, \square, \square, \square, \square, \square, \square, \square, \square$ . The 2D grid is a 10x10 grid of squares. The mapping is:  $\square \rightarrow \square_{1,1}, \square \rightarrow \square_{1,2}, \square \rightarrow \square_{1,3}, \square \rightarrow \square_{1,4}, \square \rightarrow \square_{1,5}, \square \rightarrow \square_{1,6}, \square \rightarrow \square_{1,7}, \square \rightarrow \square_{1,8}, \square \rightarrow \square_{1,9}, \square \rightarrow \square_{1,10}$ .

Part (b) shows a 1D sequence of 10 elements (represented by squares) being mapped to a 2D grid of 10 rows and 10 columns. The mapping is shown by a sequence of arrows pointing from the 1D elements to the 2D grid. The 1D sequence is:  $\square, \square, \square, \square, \square, \square, \square, \square, \square, \square$ . The 2D grid is a 10x10 grid of circles. The mapping is:  $\square \rightarrow \square_{1,1}, \square \rightarrow \square_{1,2}, \square \rightarrow \square_{1,3}, \square \rightarrow \square_{1,4}, \square \rightarrow \square_{1,5}, \square \rightarrow \square_{1,6}, \square \rightarrow \square_{1,7}, \square \rightarrow \square_{1,8}, \square \rightarrow \square_{1,9}, \square \rightarrow \square_{1,10}$ .

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$$\frac{1}{2} \left( \frac{1}{2} + \frac{1}{2} \right) = \frac{1}{2}$$
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表1. Lineage-negative (Lin<sup>-</sup>) CSC及び早期関与細胞 (ECC) の同定

マーカー	L i n - C S C	E C C	標識
造血細胞系			
G A T A 1 §	不在	不在	直接
G A T A 2 §	不在	不在	直接
C D 4 5 *	不在	不在	直接
C D 4 5 R O *	不在	不在	直接
C D 8 *	不在	不在	直接
C D 2 0 *	不在	不在	直接
グリコホリン A *	不在	不在	直接
骨格筋細胞系			
M y o D §	不在	不在	直接
ミオゲニン §	不在	不在	直接
M y f 5 §	不在	不在	直接
骨格筋ミオシン †	不在	不在	直接
神経細胞系			
神経フィラメント 2 0 0 †	不在	不在	直接
G F A P §	不在	不在	間接的
M A P 1 b §	不在	不在	間接的
筋細胞系			
G A T A 4 §	不在	存在	間接的
N k x 2 . 5 ‡	不在	存在	間接的
M E F 2 C ‡	不在	存在	間接的
心筋ミオシン †	不在	存在	間接的 / Q D
α - 筋節アクチン	不在	存在	間接的 / Q D
ネスチン	不在	存在	間接的
デスミン	不在	存在	間接的
コネキシン 4 3	不在	存在	間接的 / Q D
N - カドヘリン	不在	存在	間接的 / Q D
血管平滑筋細胞系			
G A T A 4 §	不在	存在	直接
G A T A 6 ‡	不在	存在	直接
α - 平滑筋アクチン †	不在	存在	間接的 / Q D
T G F β 1 レセプター	不在	存在	間接的
内皮細胞系			
G A T A 4 §	不在	存在	直接
E s t 1 ‡	不在	存在	直接
E r g 1 ‡	不在	存在	直接
ビメンチン	不在	存在	間接的
フォン・ヴィレブランド因子 †	不在	存在	間接的 / Q D
V E - カドヘリン	不在	存在	間接的
F l k 1	不在	存在	間接的

表 1. 直接標識法は蛍光色素結合一次抗体の使用に相当し、間接的標識法は、非結合一次抗体と蛍光色素結合二次抗体の使用に相当する。蛍光色素結合一次抗体の混合物を使用した：\*カクテル 1、§カクテル 2、†カクテル 3、‡カクテル 4。QD は、量子ドット (QD) による一次抗体の直接標識を示す。間接的/QD は、間接的標識及び QD を伴う直接標識の両方を使用したことを示す。

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表 2. FACS 分析用抗体

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rMy12-S: CCTCTAGTGGCTCTACTGTAGGCTTC (26mer, 融点55℃)

rMy12-A: TTCCACTTACTTCCACTCCGAGTCC (25mer, 融点 59℃)

hMLC2-S: GACGTGACTGGCAACTTGGACTAC (24mer、融点57℃)

hMLC2-A: TGTCGTGACCAAATACACGACCTC (24mer、融点58℃)

ARC-261r: GAGACGGAGTCTCGCTCTGTCGC (23mer、融点61℃)

表3：各試料を、15  $\mu$  LのPlatinum PCR Blue Mix溶液（Invitrogen）及び0.2  $\mu$  Mの各プライマーと混合し、PCTを実施した。PCR反応は次のように実施した：94℃で30秒間；94℃で30秒間、60℃で30秒間、及び72℃で1分間のサイクルを35回；72℃で3分間。PCR産物は2%アガロースゲル電気泳動で分離した。

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$\frac{1}{n} \sum_{i=1}^n \left( \frac{\partial L(\theta)}{\partial \theta_i} \right)^2 = \frac{1}{n} \sum_{i=1}^n \left( \frac{\partial L(\theta)}{\partial \theta_i} \right)^2$

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Figure 2

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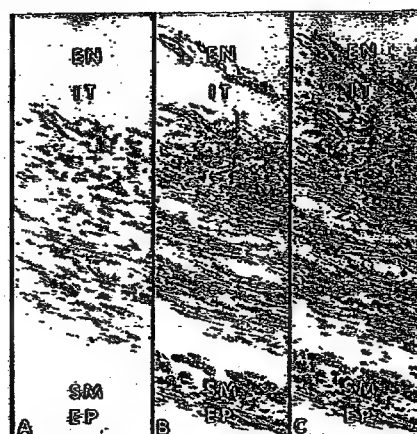


Figure 3

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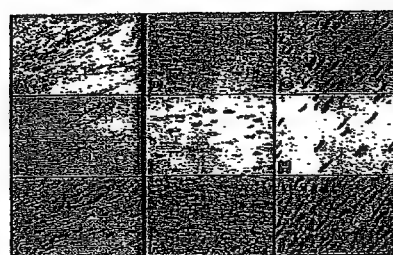


Figure 5

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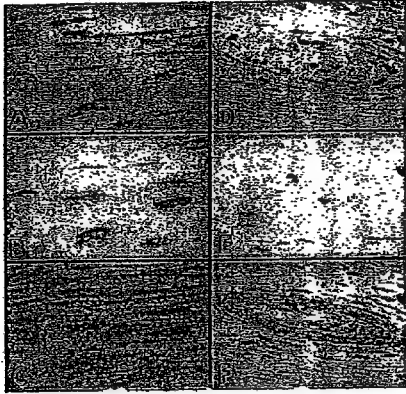


Figure 6

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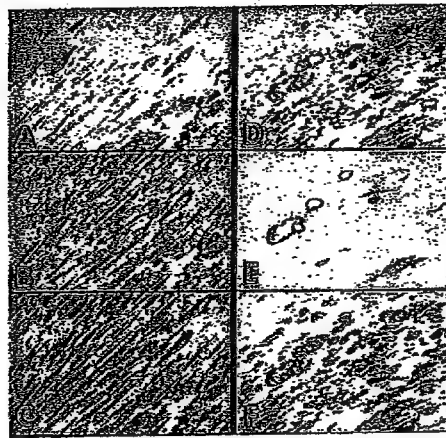


Figure 8

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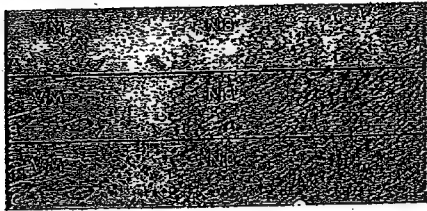


Figure 7

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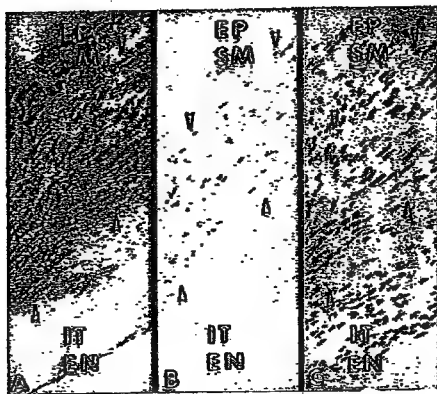


Figure 9

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Figure 10

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Figure 11

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Figure 12

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Figure 13

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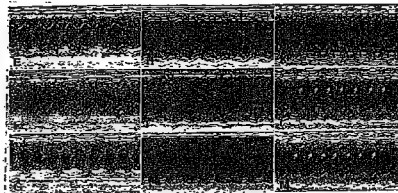


Figure 15

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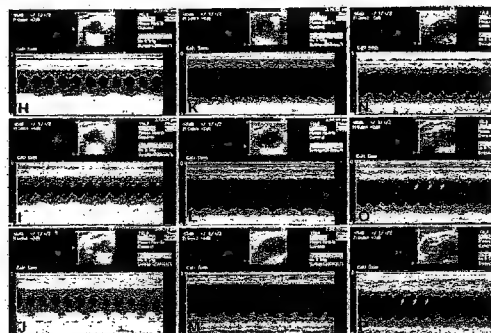


FIGURE 16

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Figure 18

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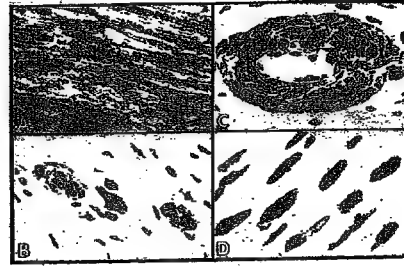


Figure 19

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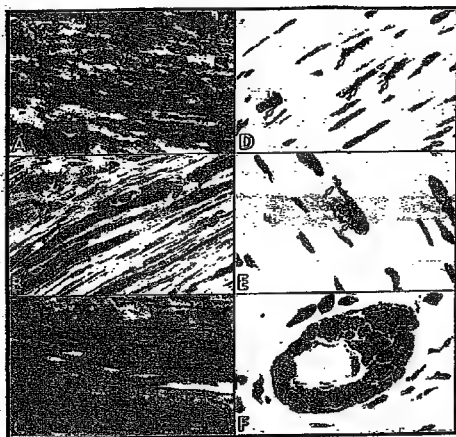


Figure 20

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Figure 21



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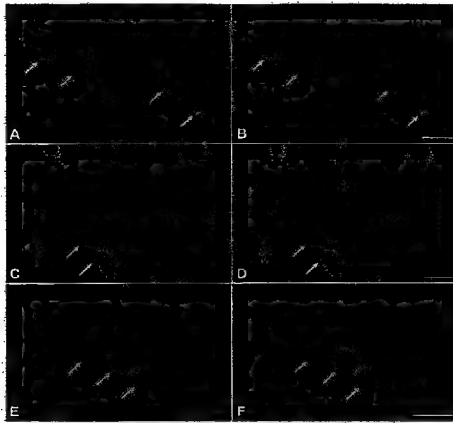


FIGURE 22A-F

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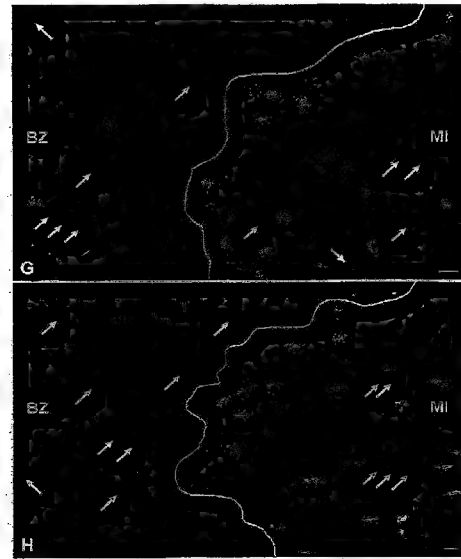


FIGURE 22G-H

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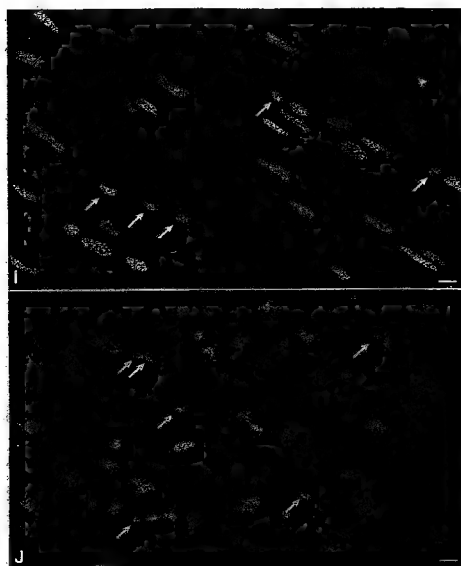


FIGURE 22I-J

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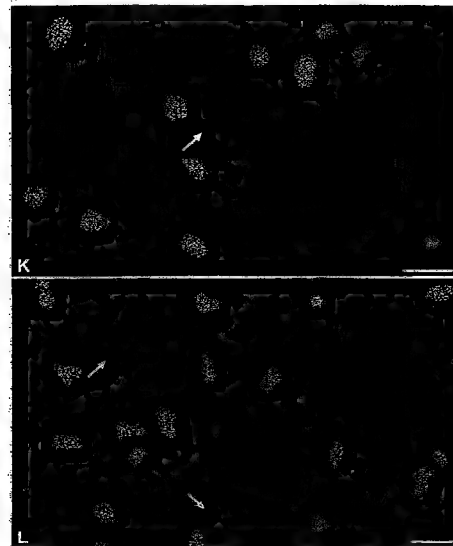


FIGURE 22K-L

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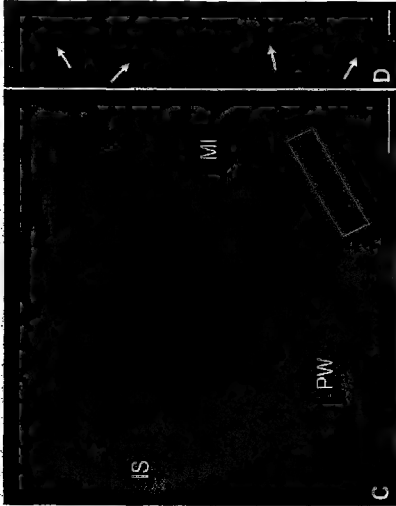


FIGURE 23C-D

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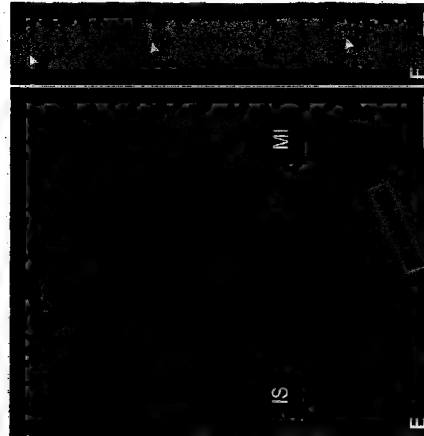


FIGURE 23E-F

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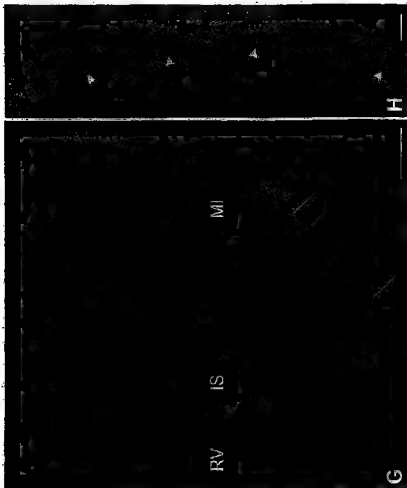


FIGURE 23G-H

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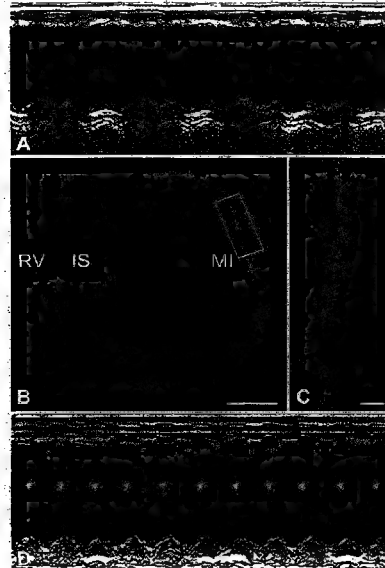


FIGURE 24A-D

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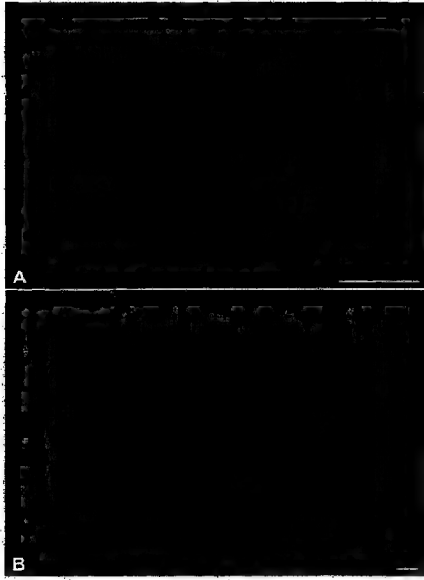


FIGURE 25A-B

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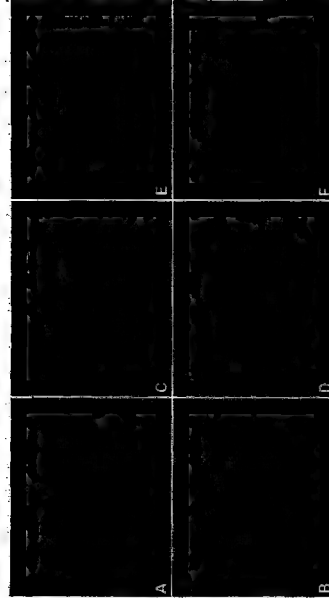


FIGURE 26A-F

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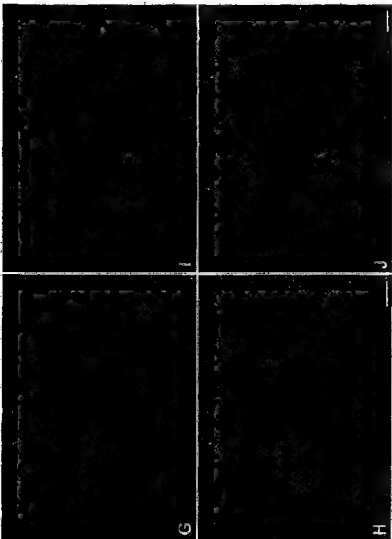


FIGURE 26G-J

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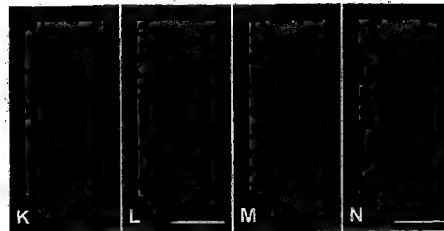


FIGURE 26K-N

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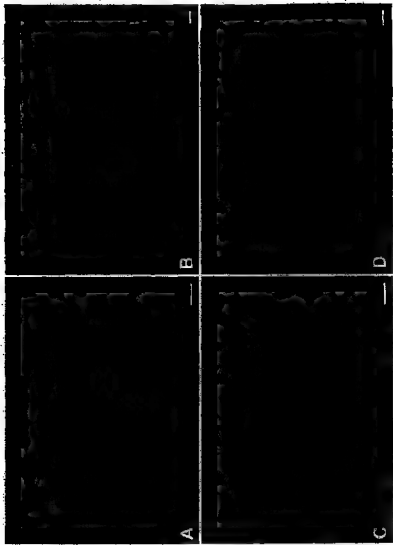


FIGURE 27A-D

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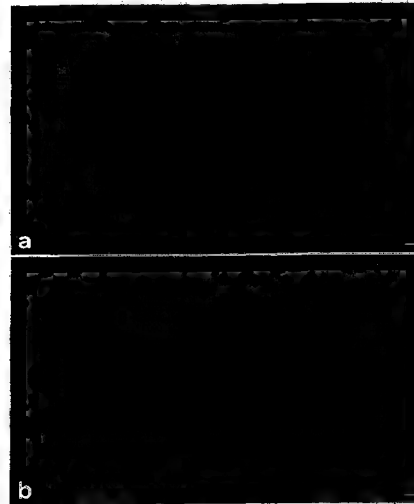


FIGURE 28A-B

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FIGURE 28C-F

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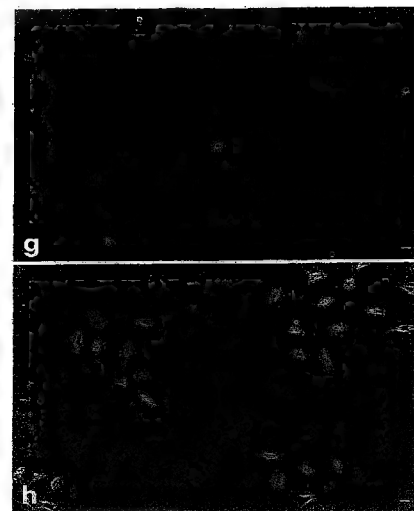


FIGURE 28G-H

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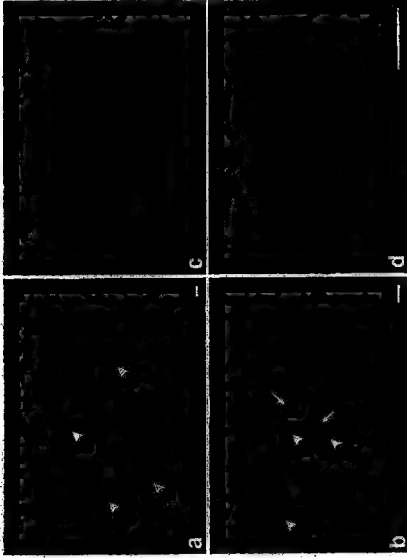


FIGURE 29A-D

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FIGURE 29E-H

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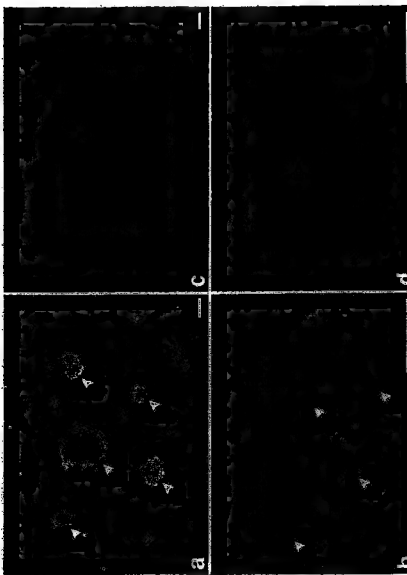


FIGURE 30A-D

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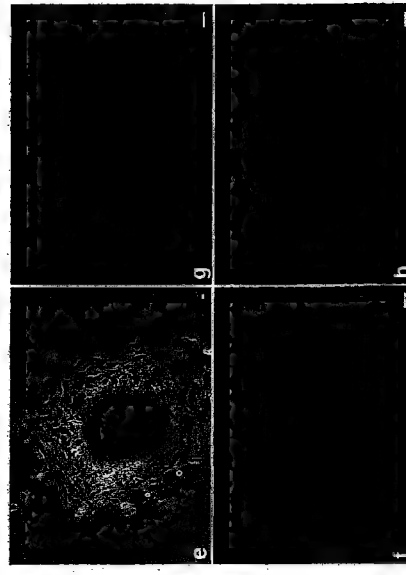


FIGURE 30E-H

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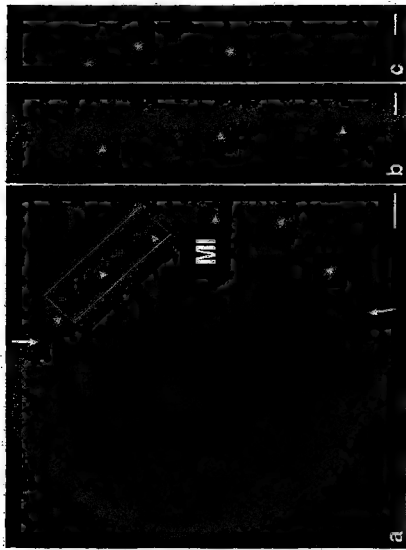


FIGURE 31A-C

□ □ □ □ □ - □ □



FIGURE 31D-E

□ □ □ □ □ - □ □

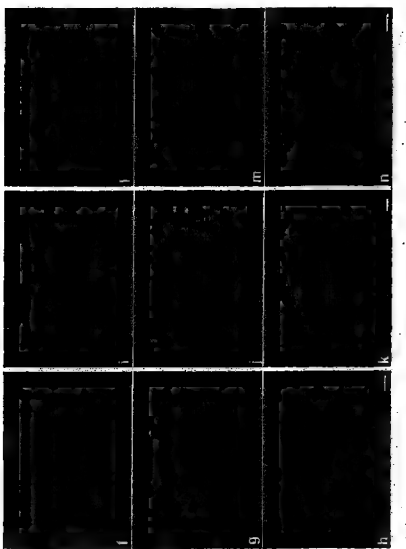


FIGURE 31F-N

□ □ □ □ □ - □ □

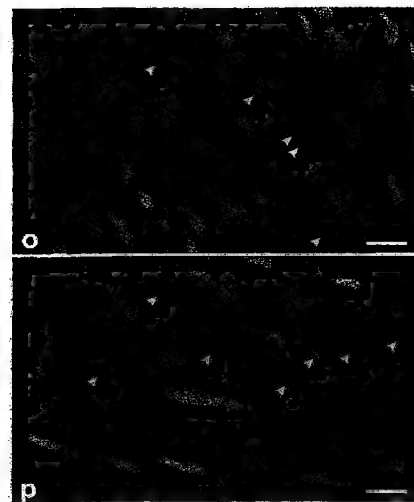


FIGURE 31O-P

□ □ □ □ □ - □ □

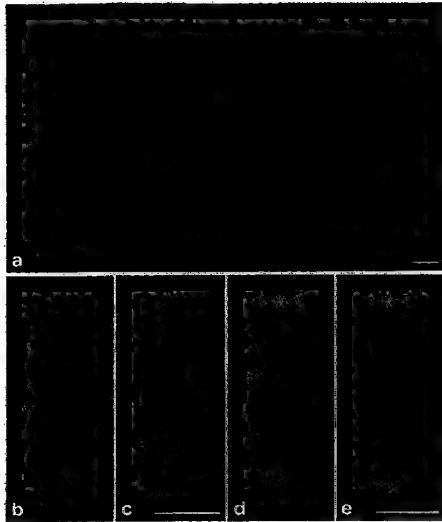


FIGURE 32A-E

□ □ □ □ □ - □ □

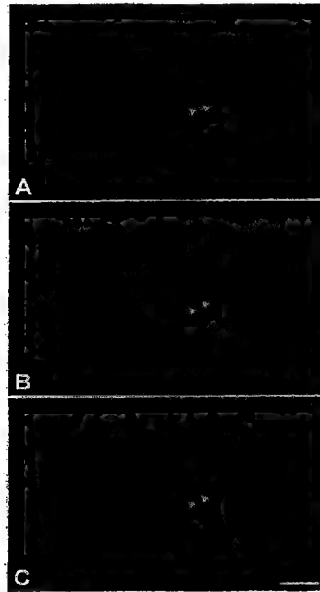


FIGURE 34A-C

□ □ □ □ □

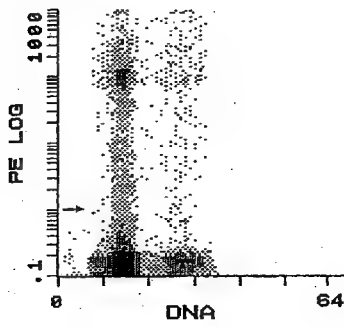


FIGURE 35

□ □ □ □ □



FIGURE 37

□ □ □ □ □

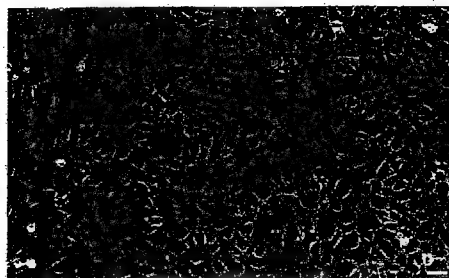


FIGURE 40

□ □ □ □ □

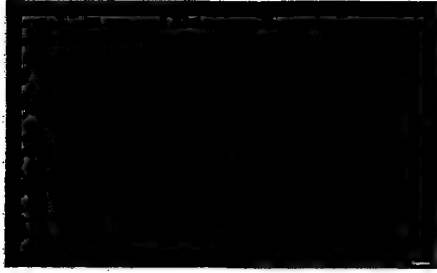


FIGURE 41

□ □ □ □ □

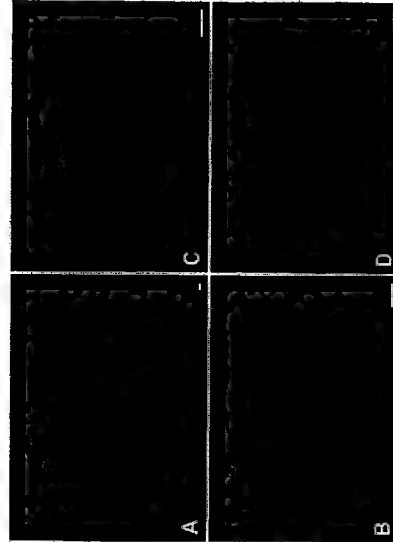


FIGURE 43

□ □ □ □ □ - □ □

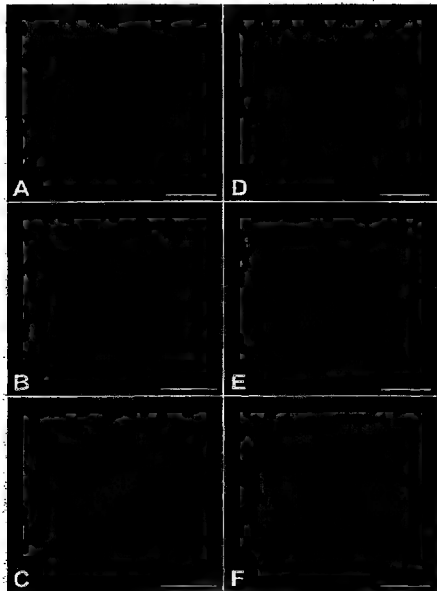


FIGURE 44A-F

□ □ □ □ □ - □ □

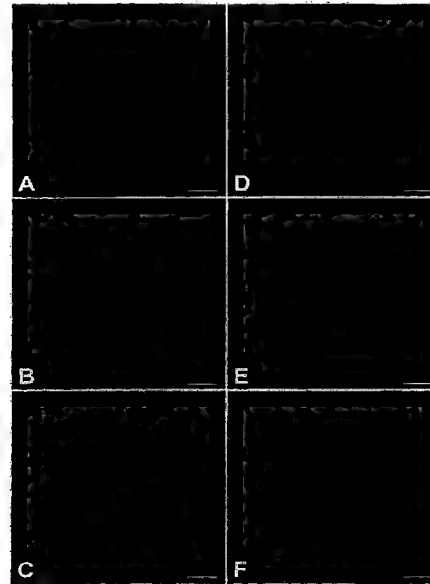


FIGURE 45A-F



□ □ □ □ □ - □ □

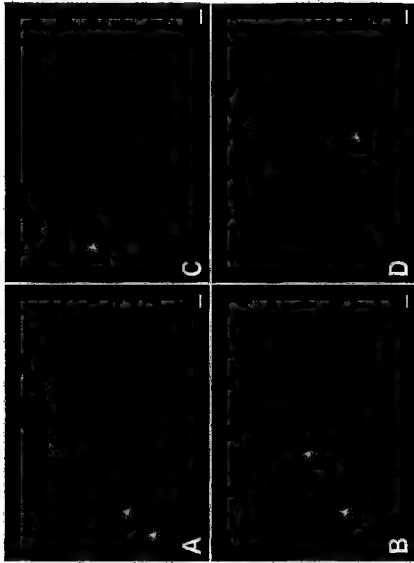


FIGURE 46A-D

□ □ □ □ □ - □ □

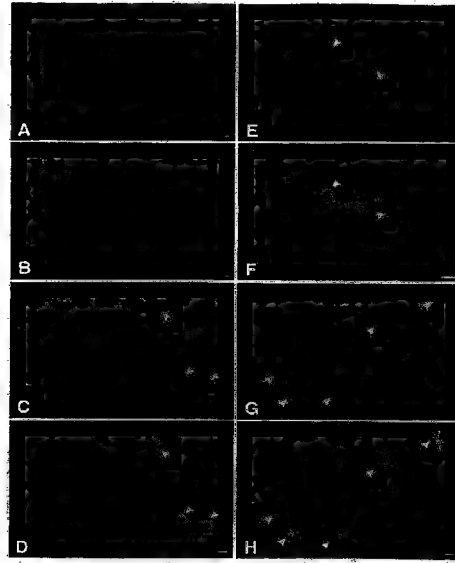


FIGURE 47A-H

□ □ □ □ □ - □ □



FIGURE 49A-B

□ □ □ □ □ - □ □

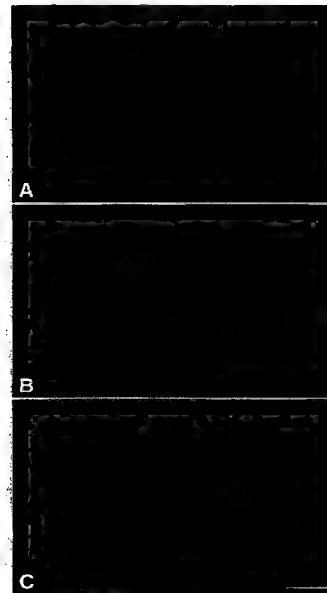


FIGURE 50A-C

□ □ □ □ □ - □ □

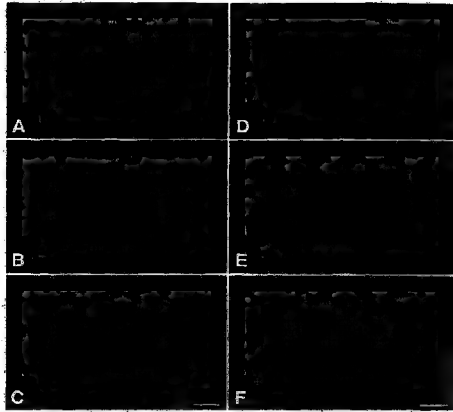


FIGURE 53A-F

□ □ □ □ □

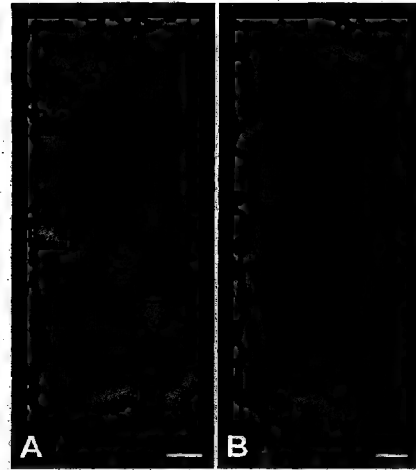


FIGURE 56

□ □ □ □ □ - □ □

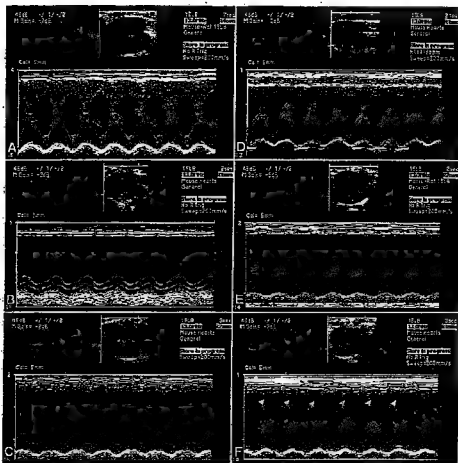


FIGURE 58A-F

□ □ □ □ □ - □ □

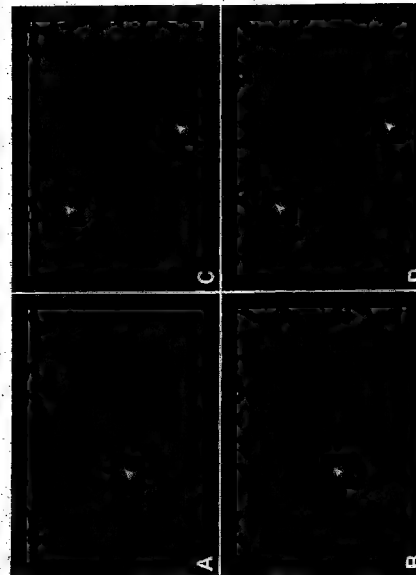


FIGURE 60A-D

□ □ □ □ □ - □ □

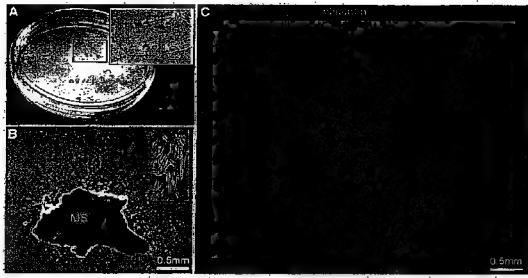


Figure 70H-C

□ □ □ □ □ - □ □

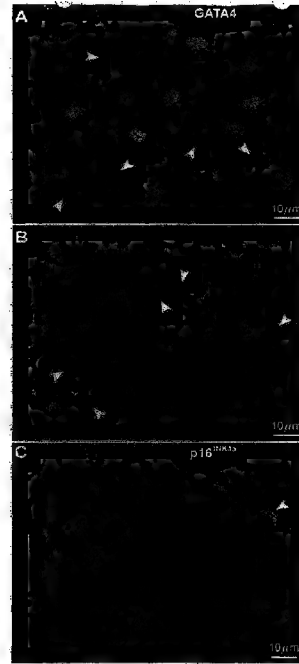


Figure 71A-C

□ □ □ □ □ - □ □

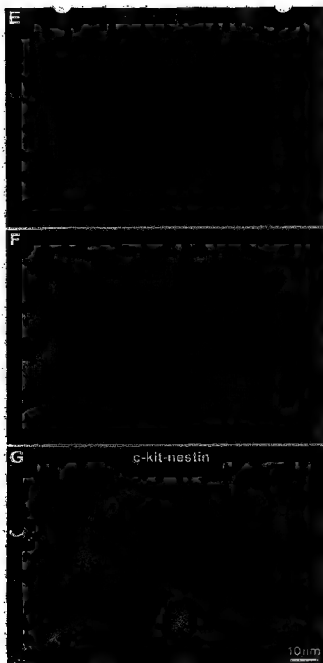


Figure 72E-G

□ □ □ □ □

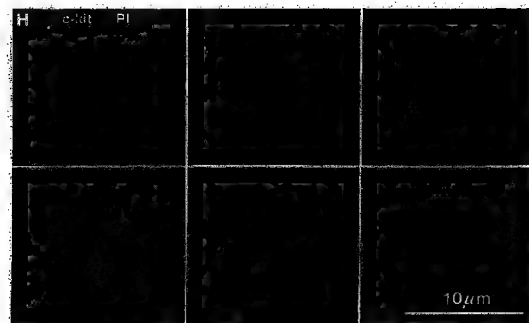


Figure 73H

□ □ □ □ □

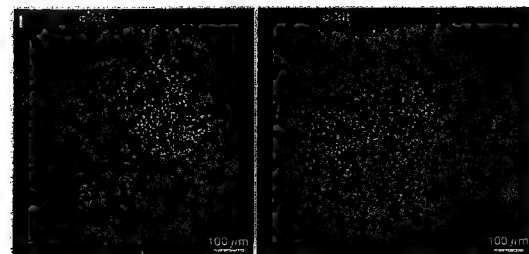


Figure 74I

□ □ □ □ □ □

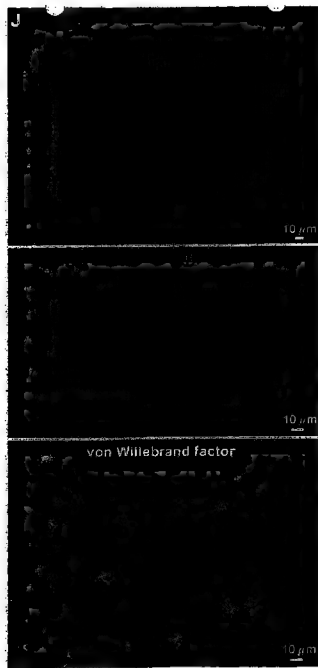


Figure 71J

□ □ □ □ □ □

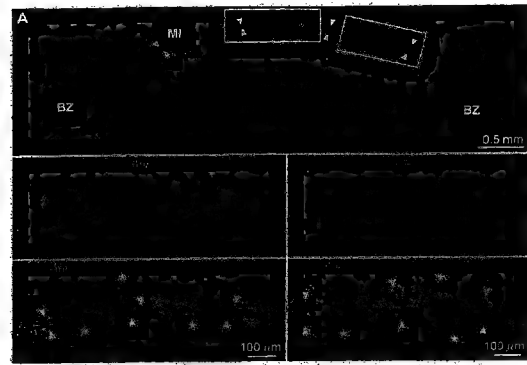


Figure 72A

□ □ □ □ □ - □ □

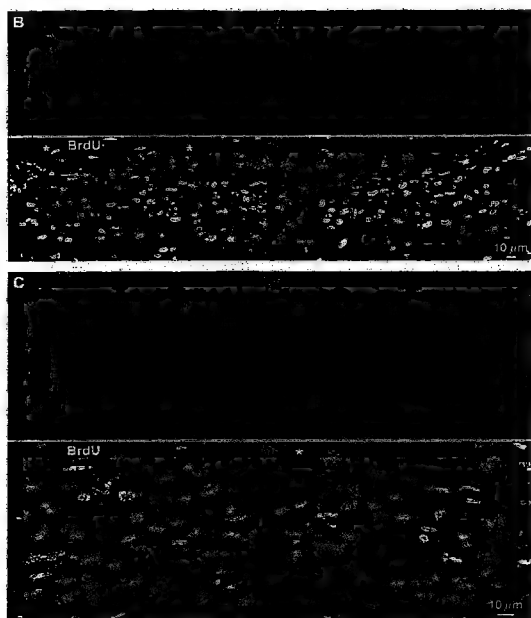


Figure 72B-C

□ □ □ □ □ - □ □



Figure 72E-H

□ □ □ □ □ - □ □

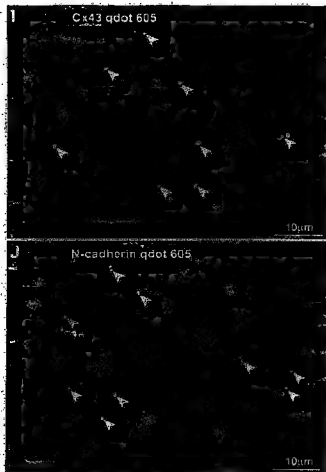


Figure 73I-J

□ □ □ □ □ - □ □

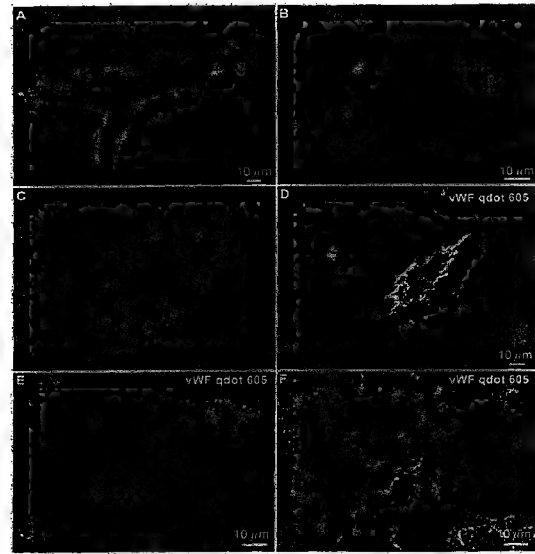


Figure 73A-F

□ □ □ □ □ □

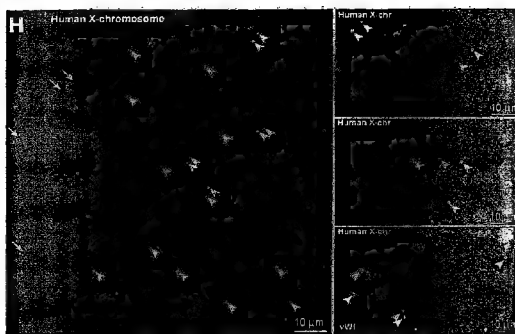


Figure 73H

□ □ □ □ □ □

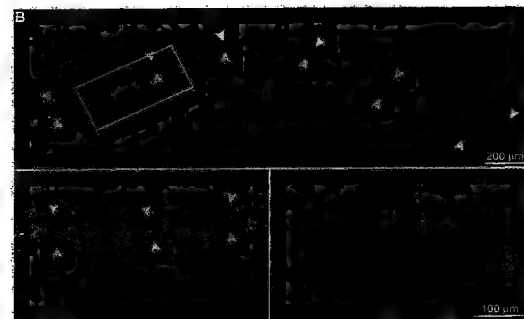


Figure 74B

□ □ □ □ □ □

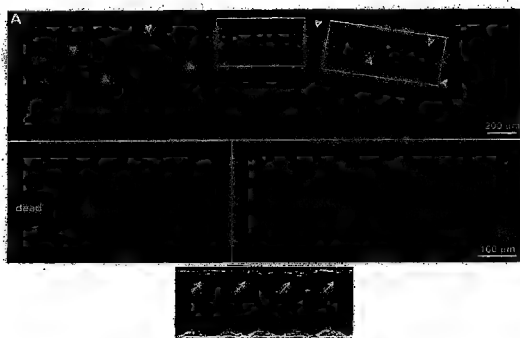


Figure 74A

□ □ □ □ □ □

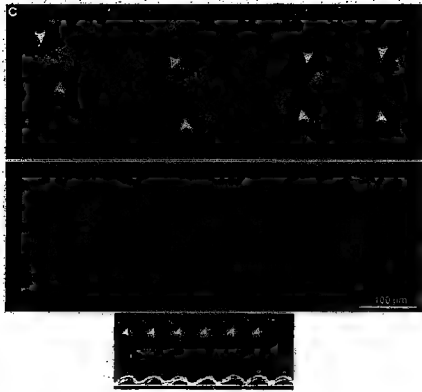


Figure 71C

□ □ □ □ □ □

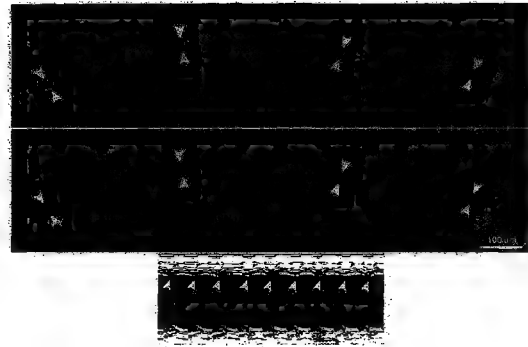


Figure 71D

□ □ □ □ □ □

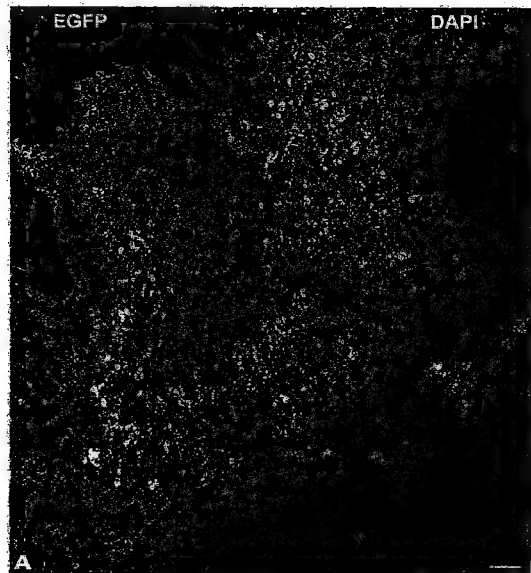


Figure 79A

□ □ □ □ □ □



Figure 79B

□ □ □ □ □ □

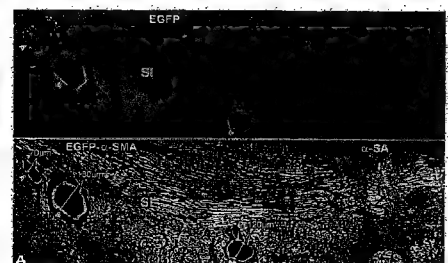


Figure 80A

□ □ □ □ □ □

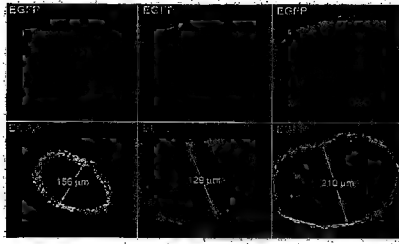


Figure 80B

□ □ □ □ □ □

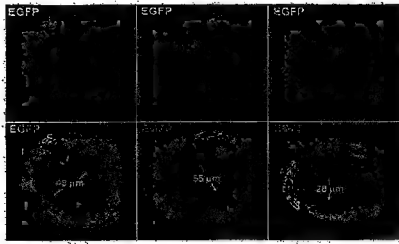


Figure 80C

□ □ □ □ □ □

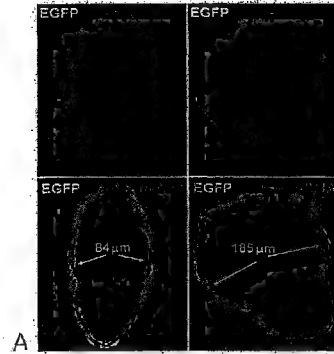
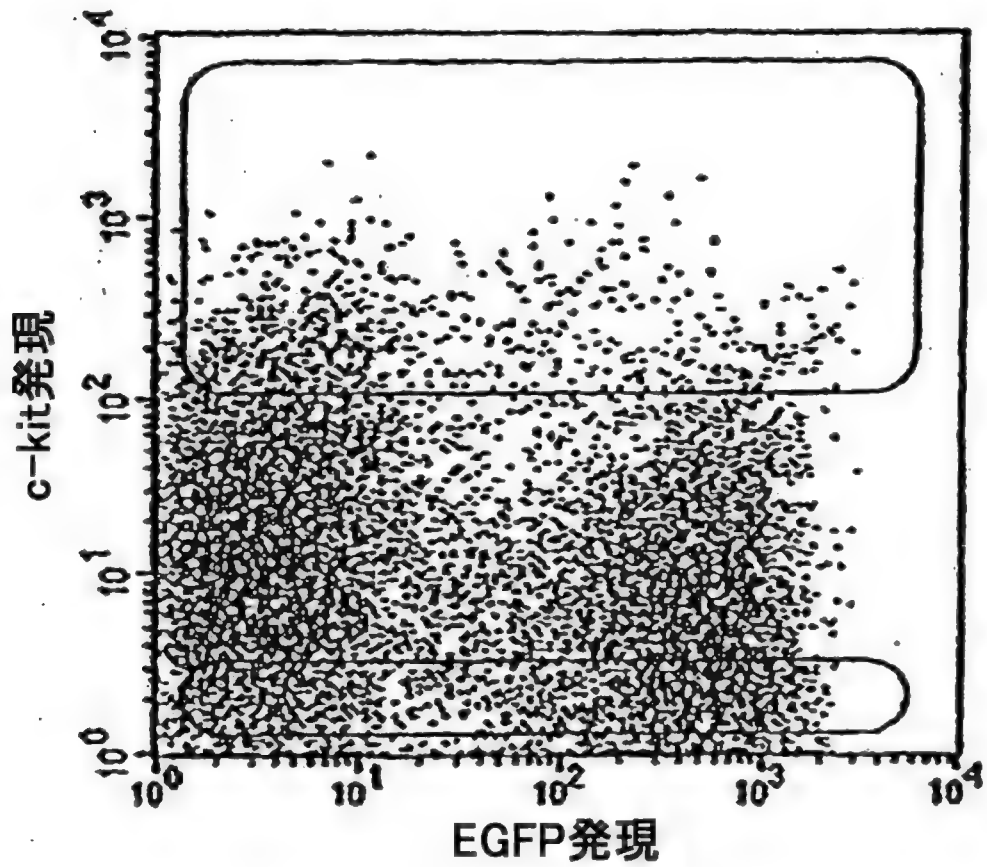


Figure 84A

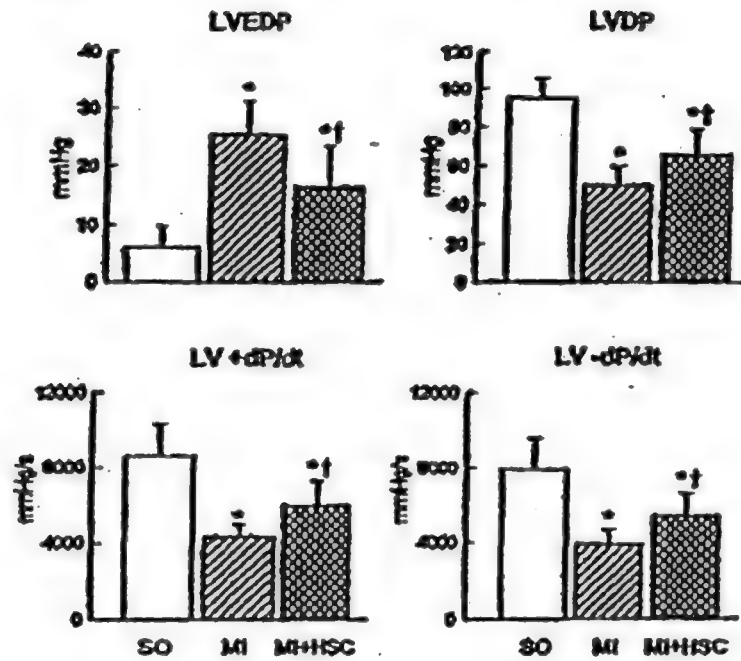
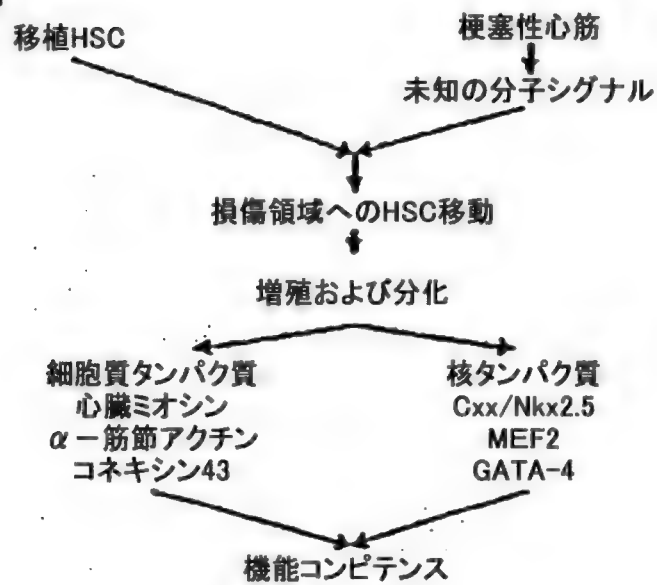
□ □ □ □



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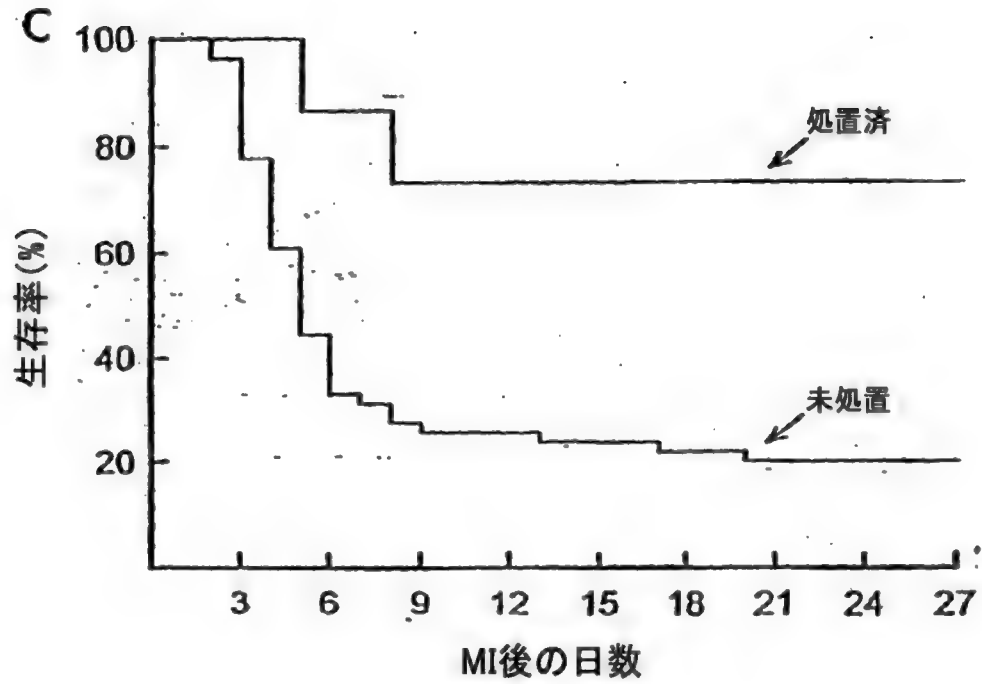
**A**

## 心室機能

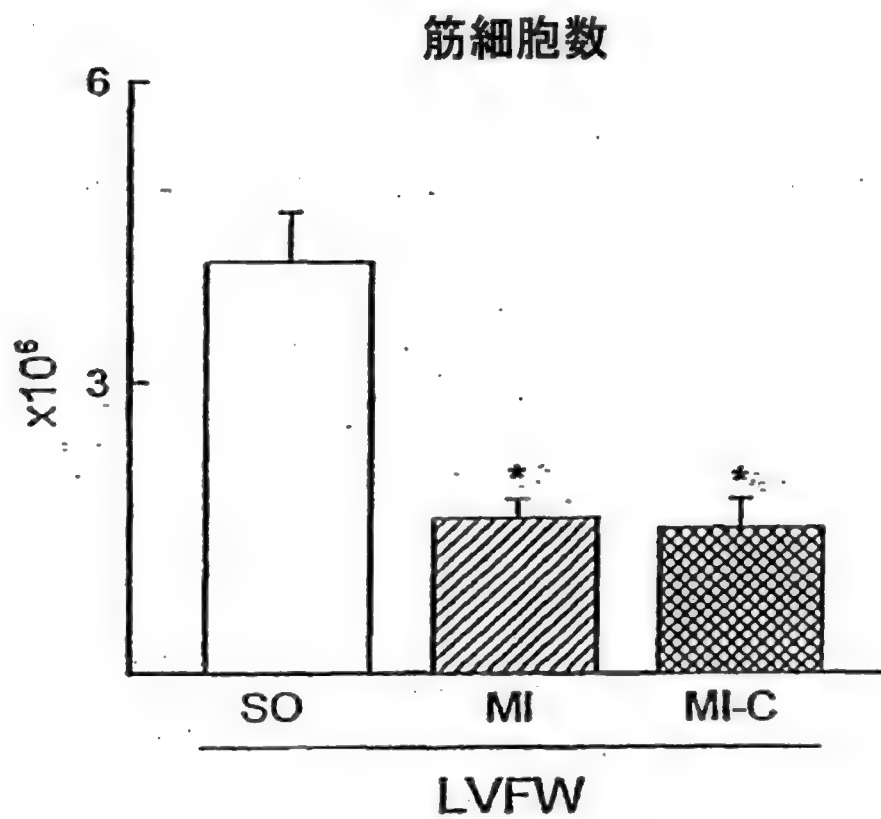
**B**



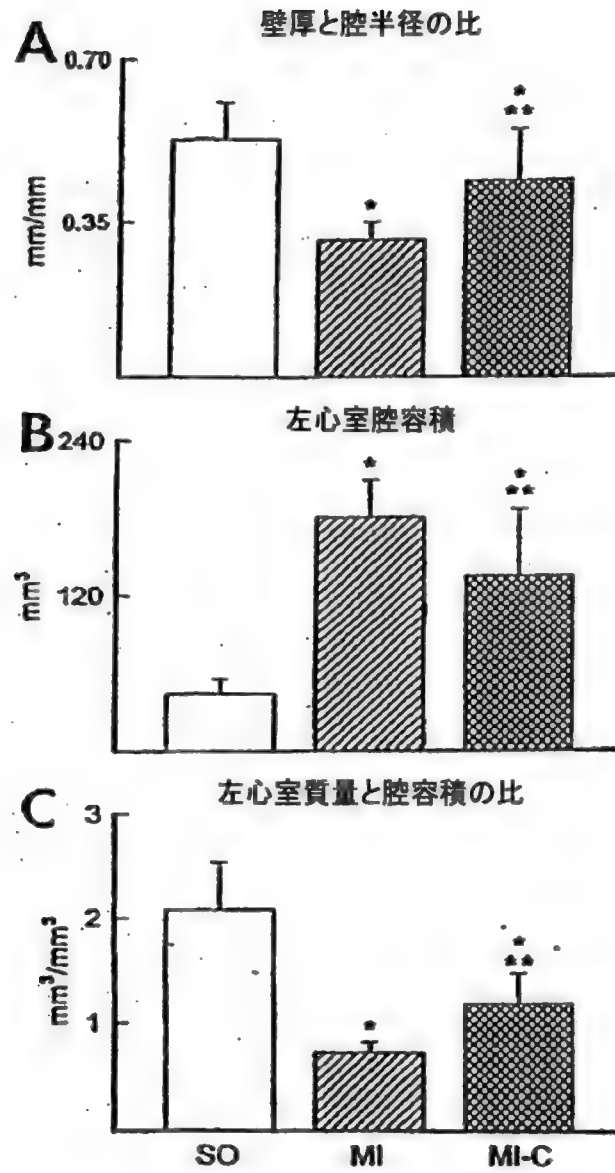
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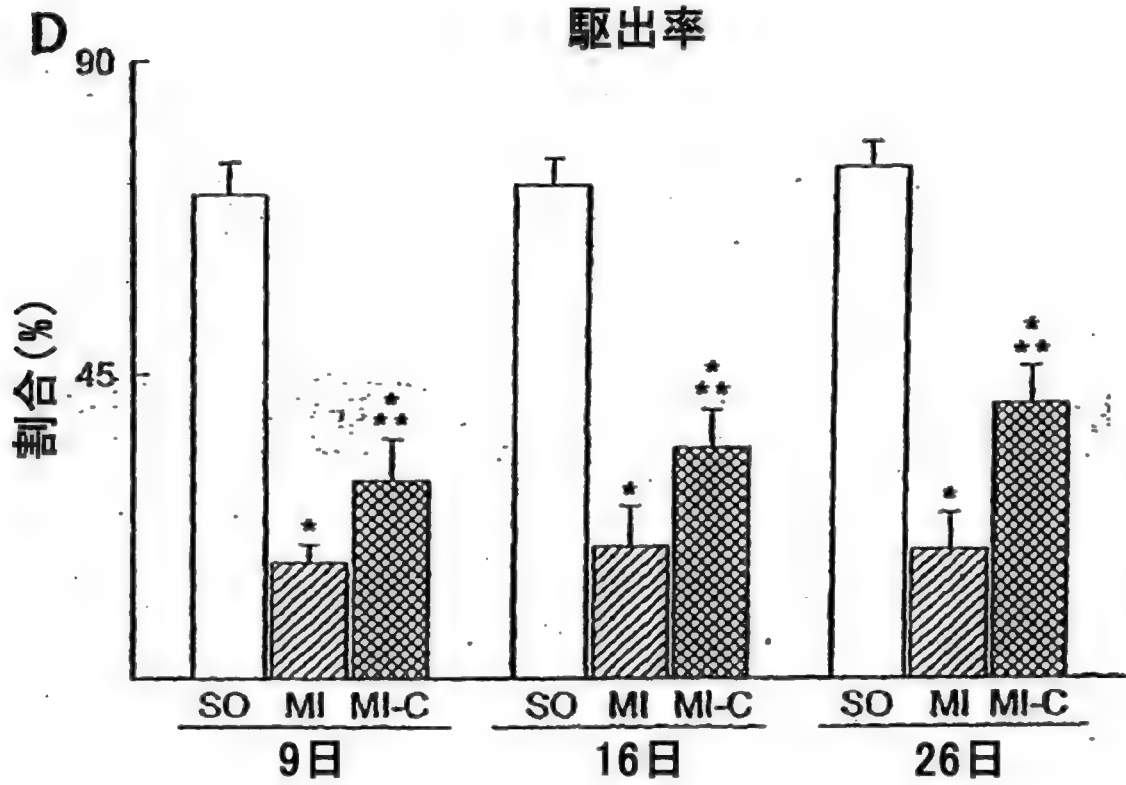
□ □ □ □ □



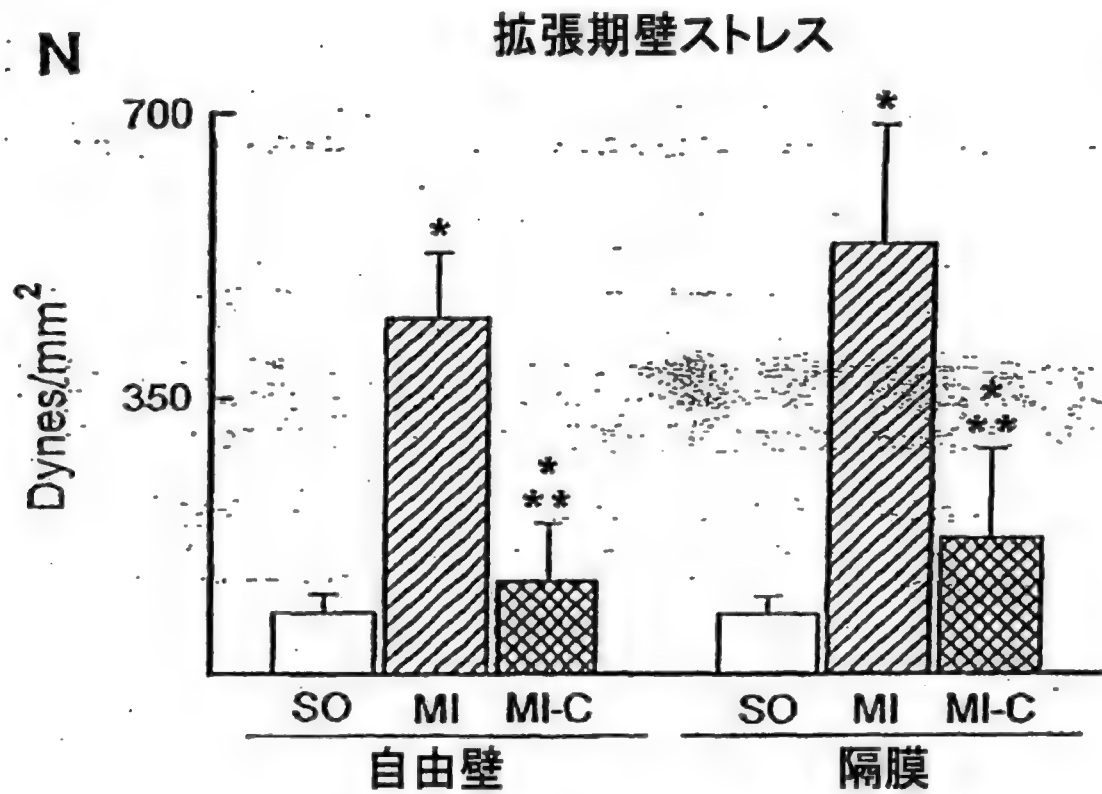
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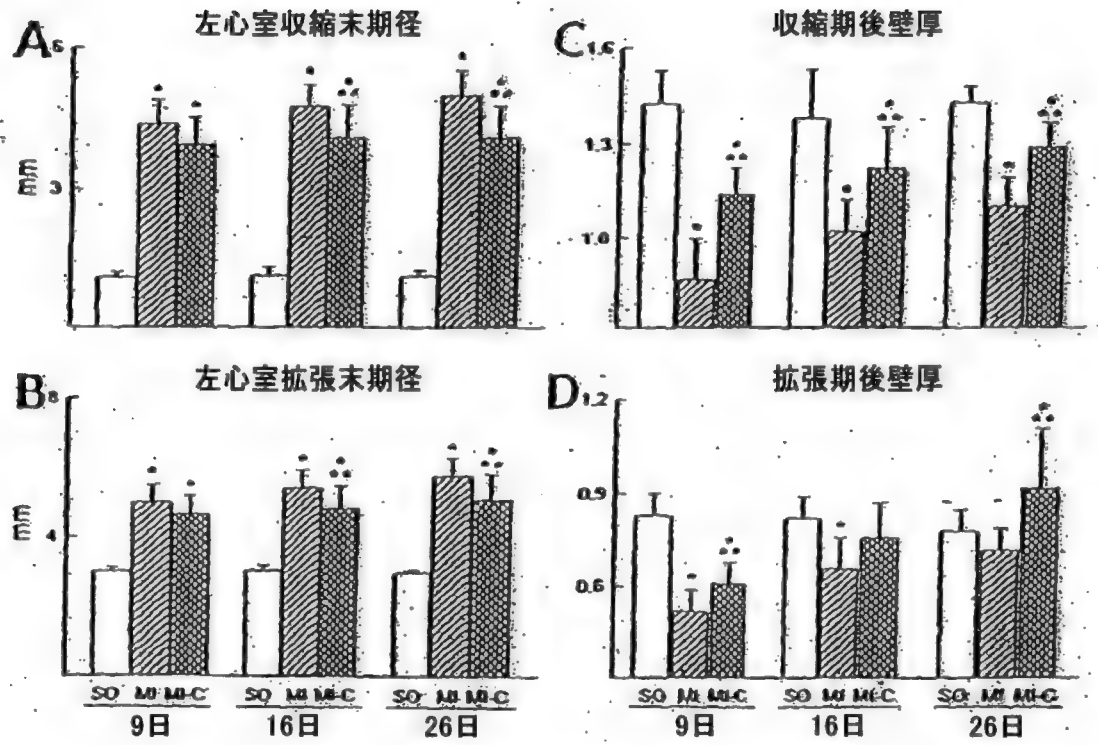
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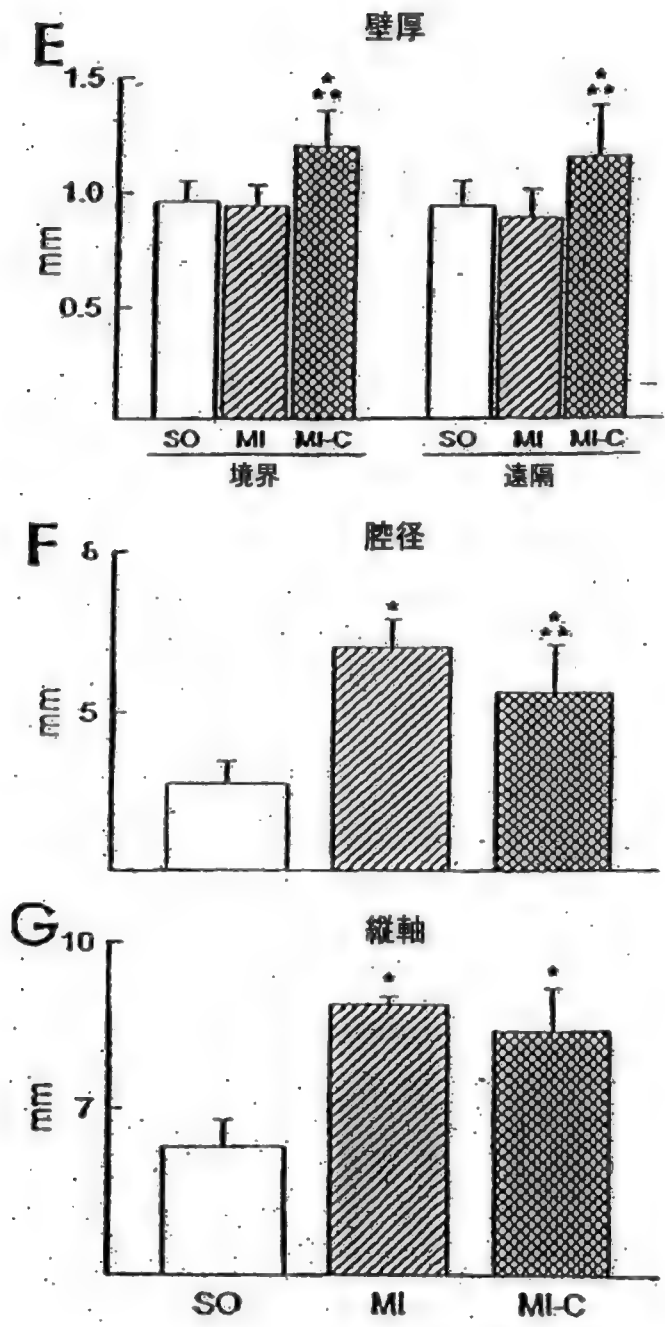
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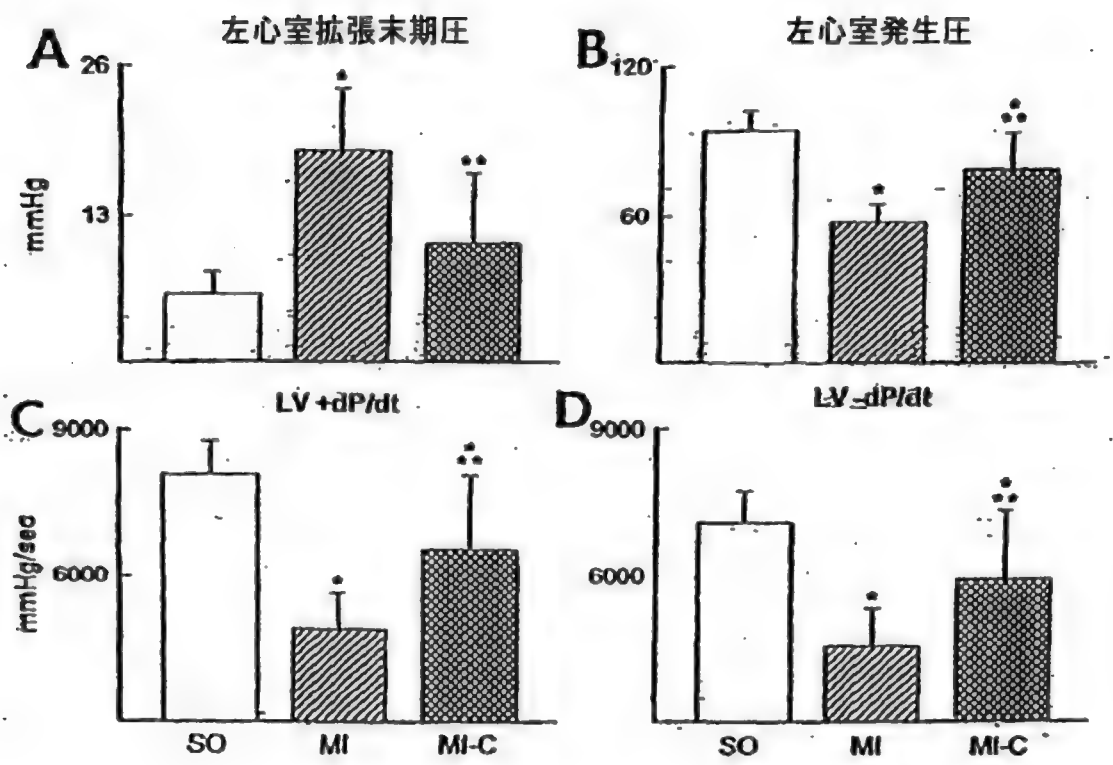
□ □ □ □ - □ □



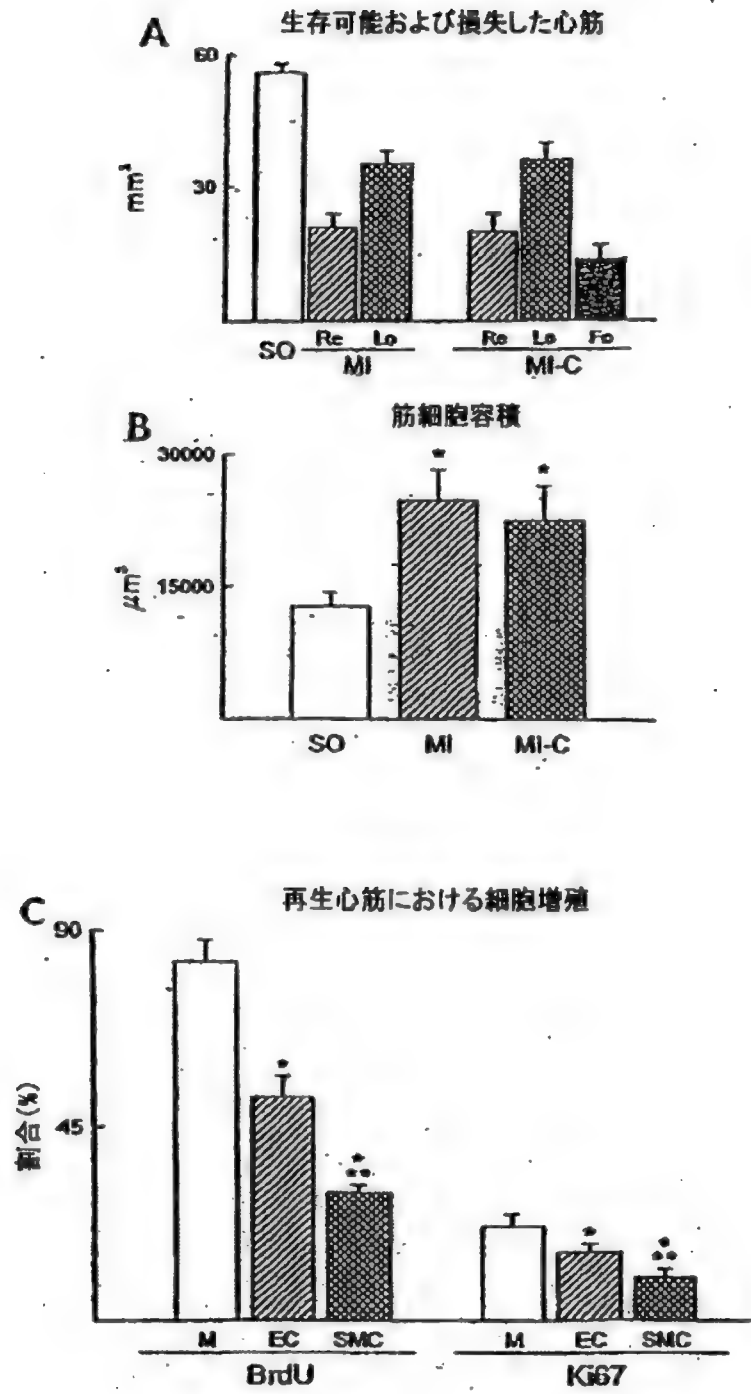
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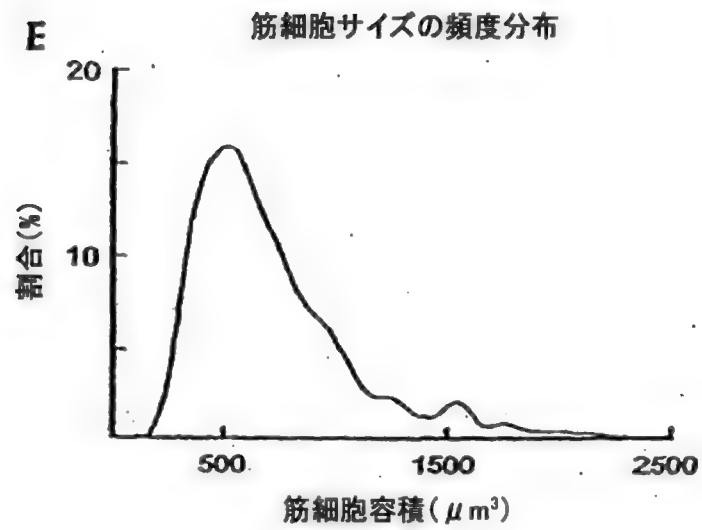
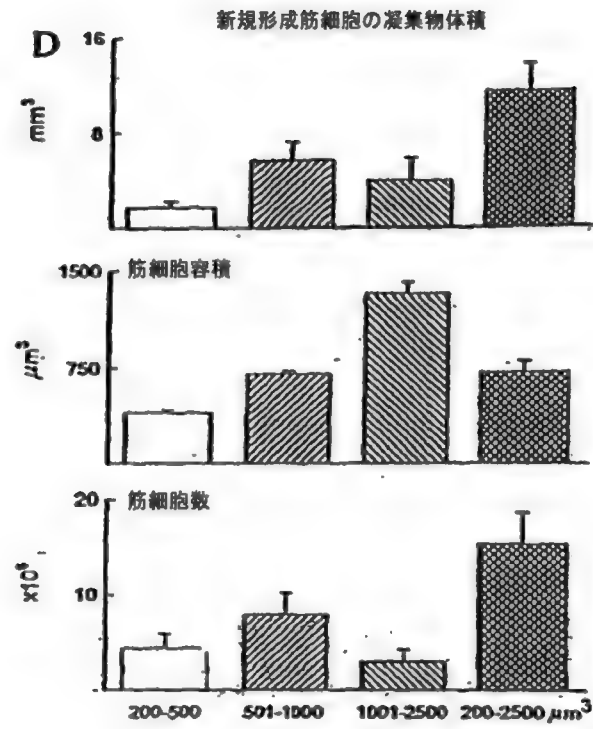
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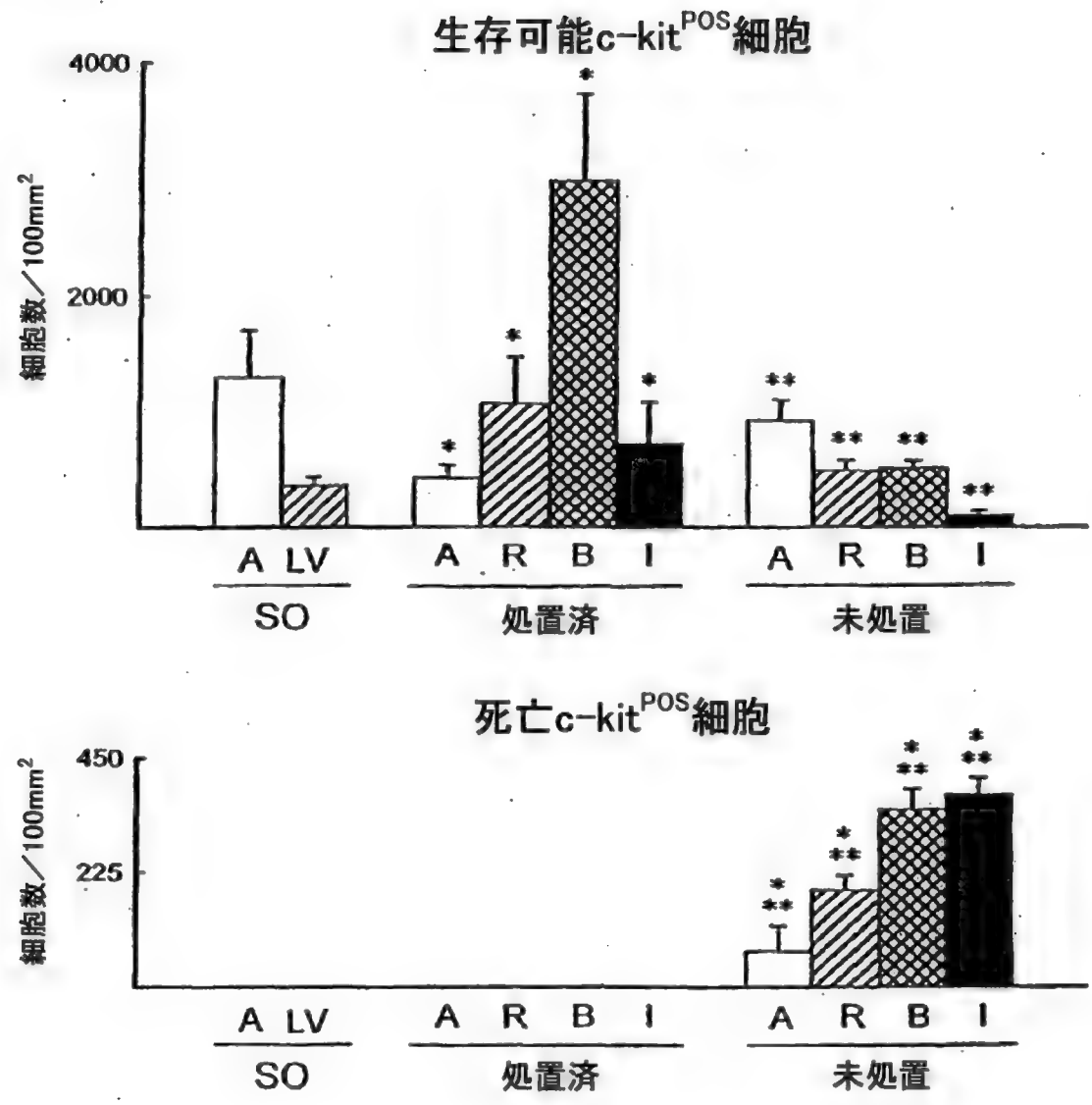


□ □ □ □ - □ □

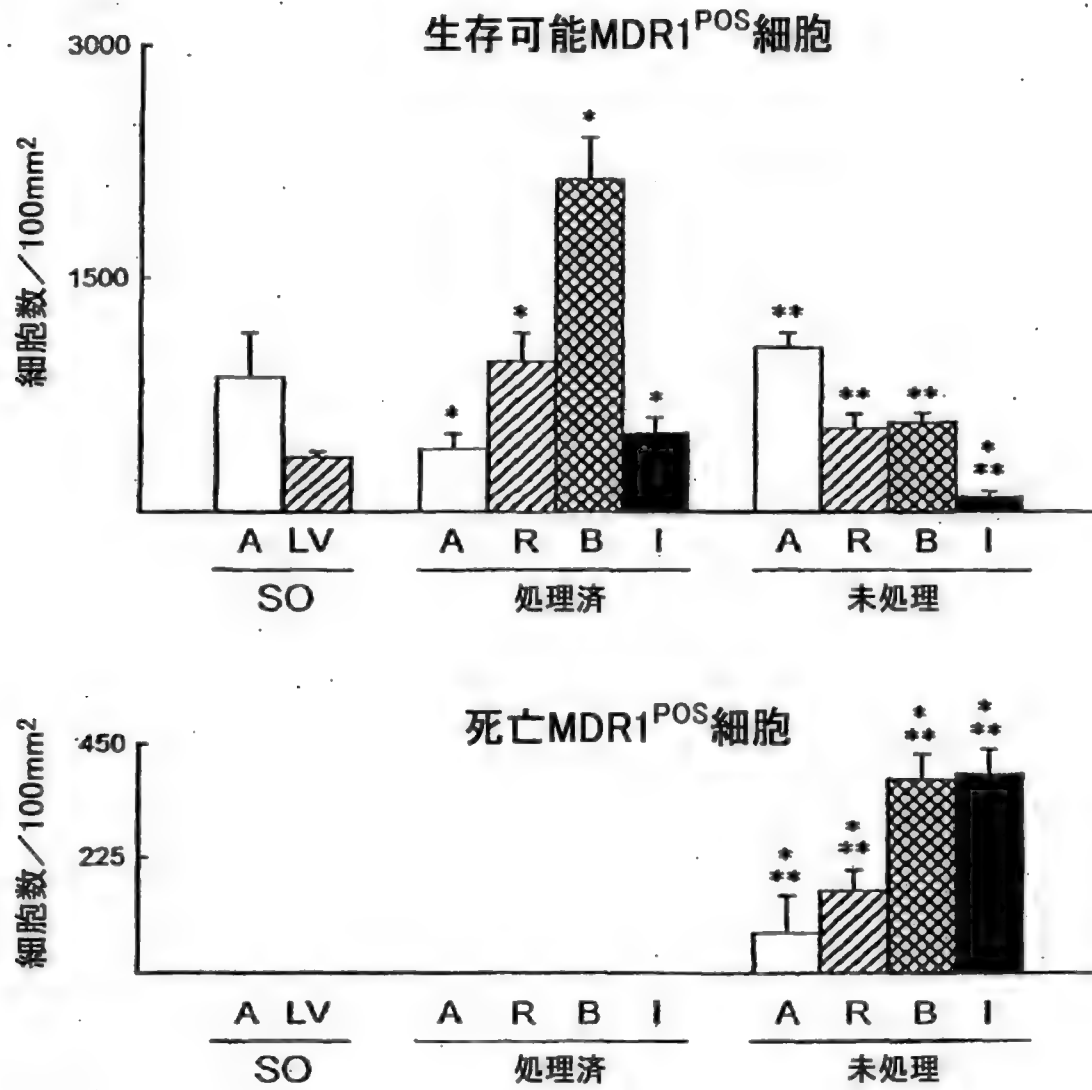




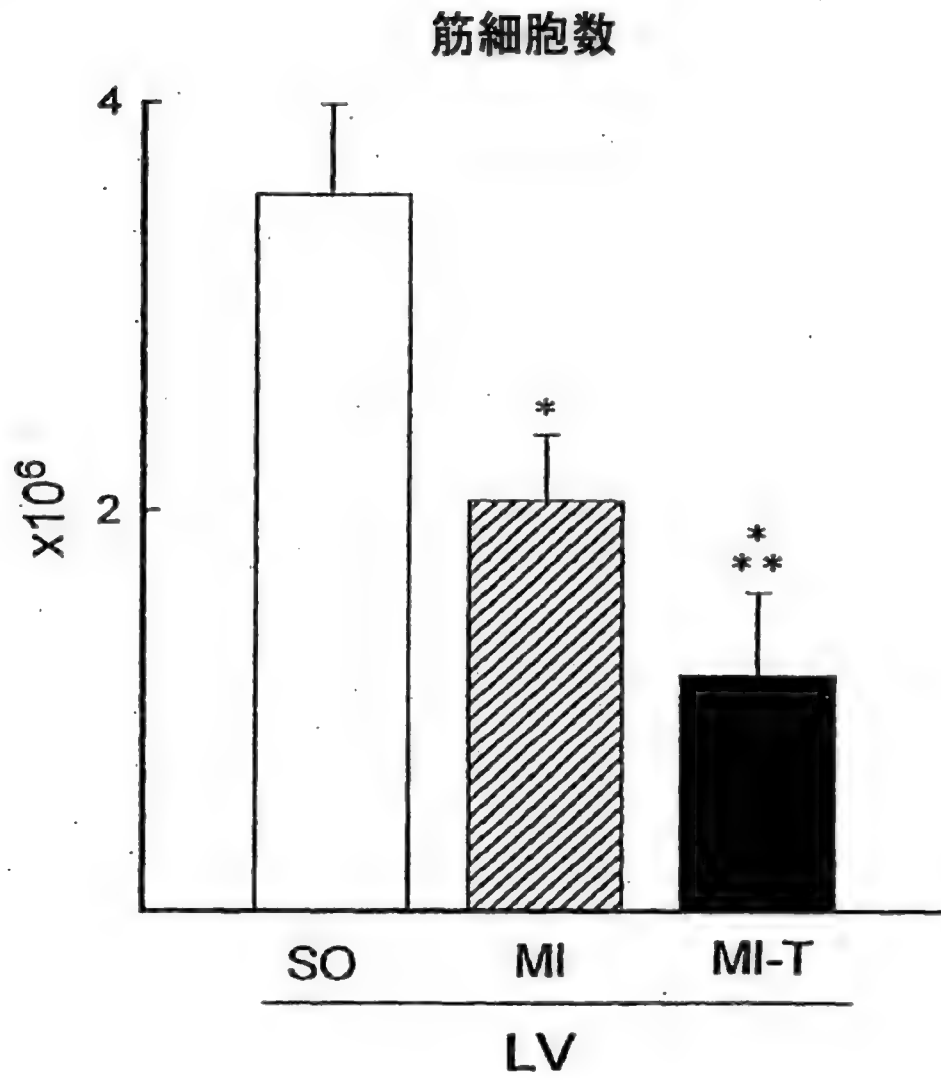
□ □ □ □ □ □



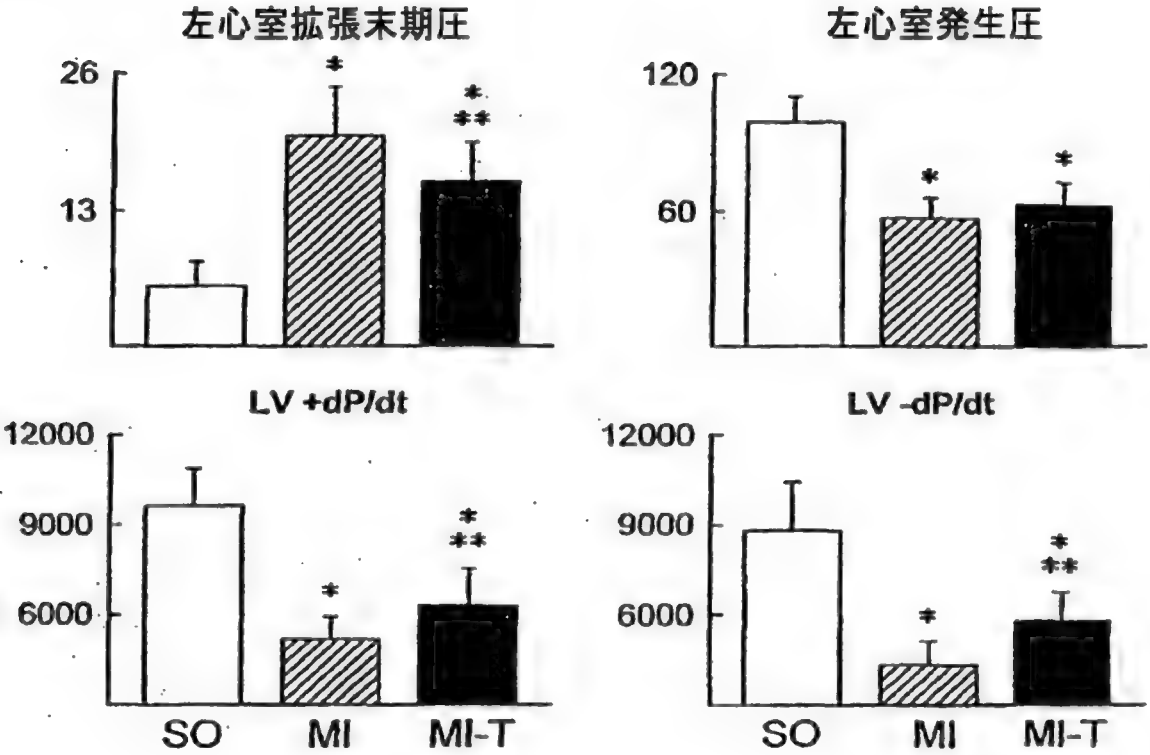
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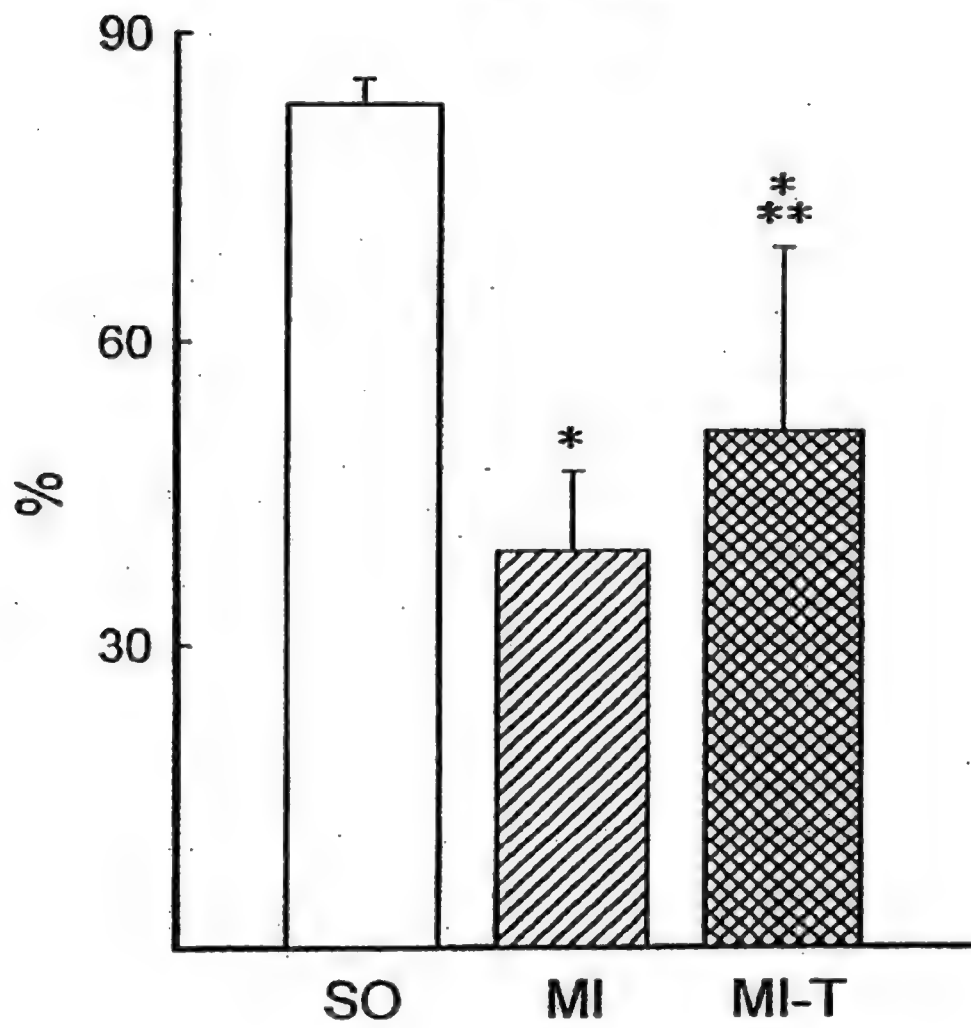


□ □ □ □ □ □

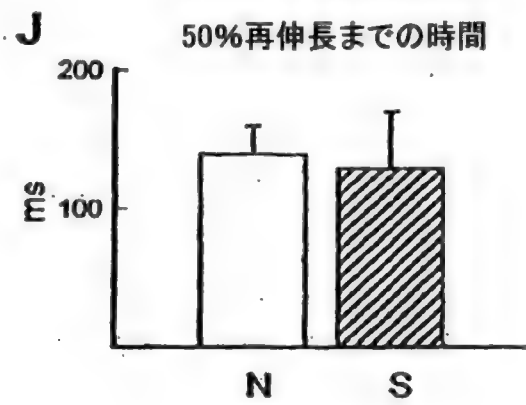
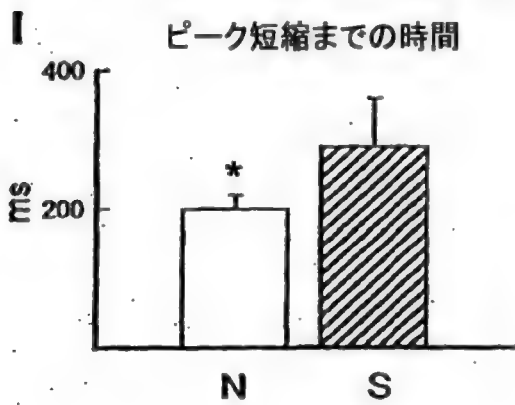
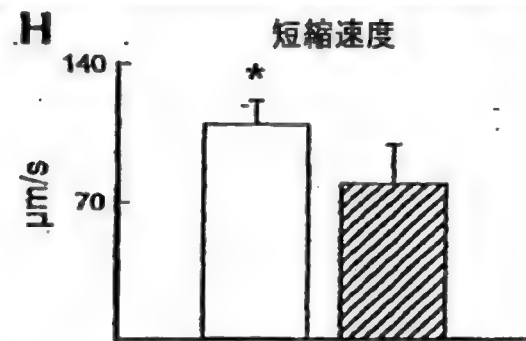
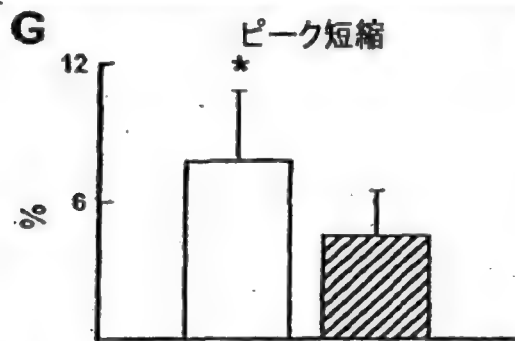
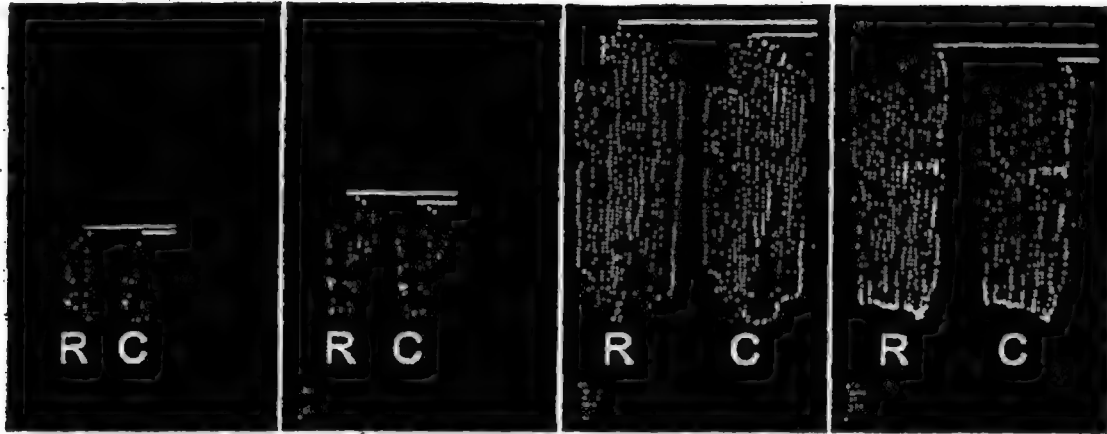


□ □ □ □ □ □

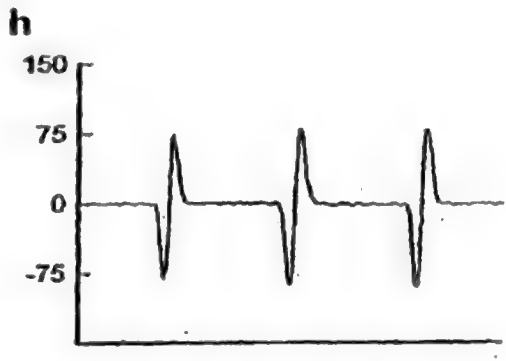
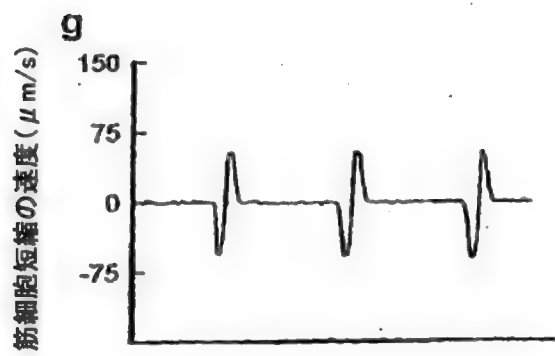
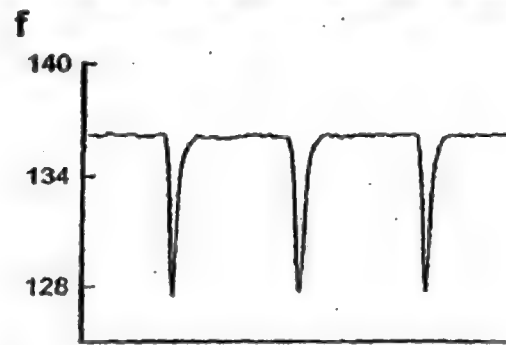
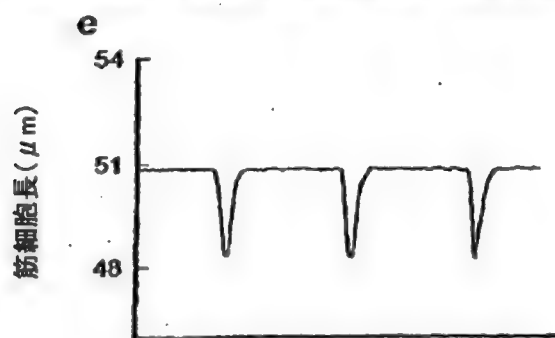
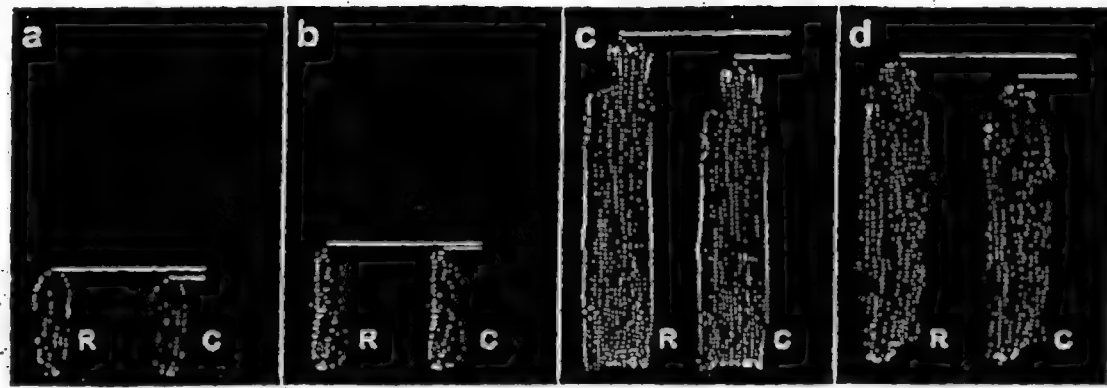
## 駆出率



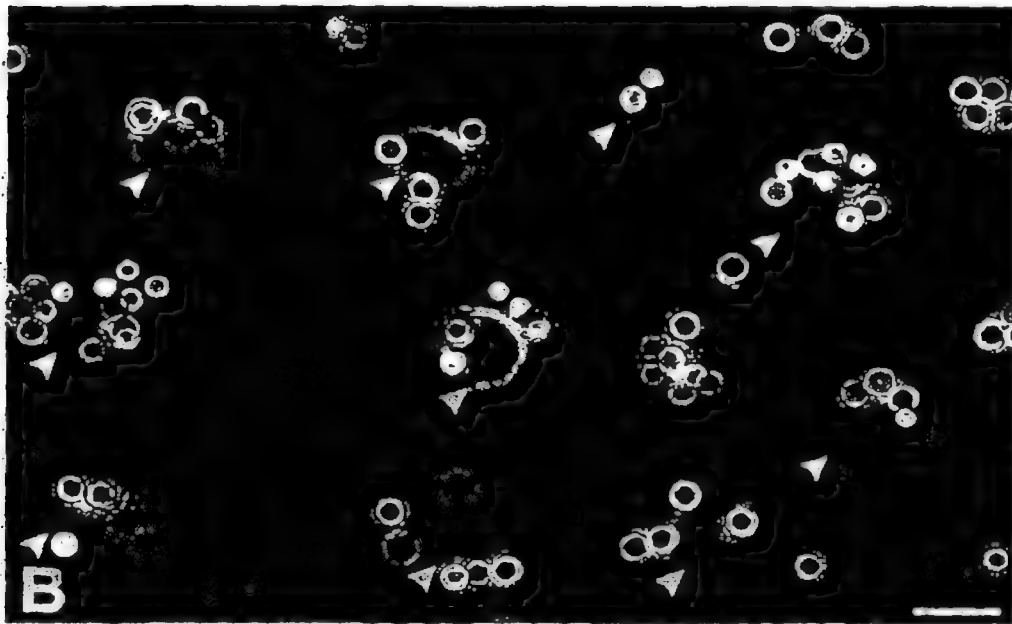
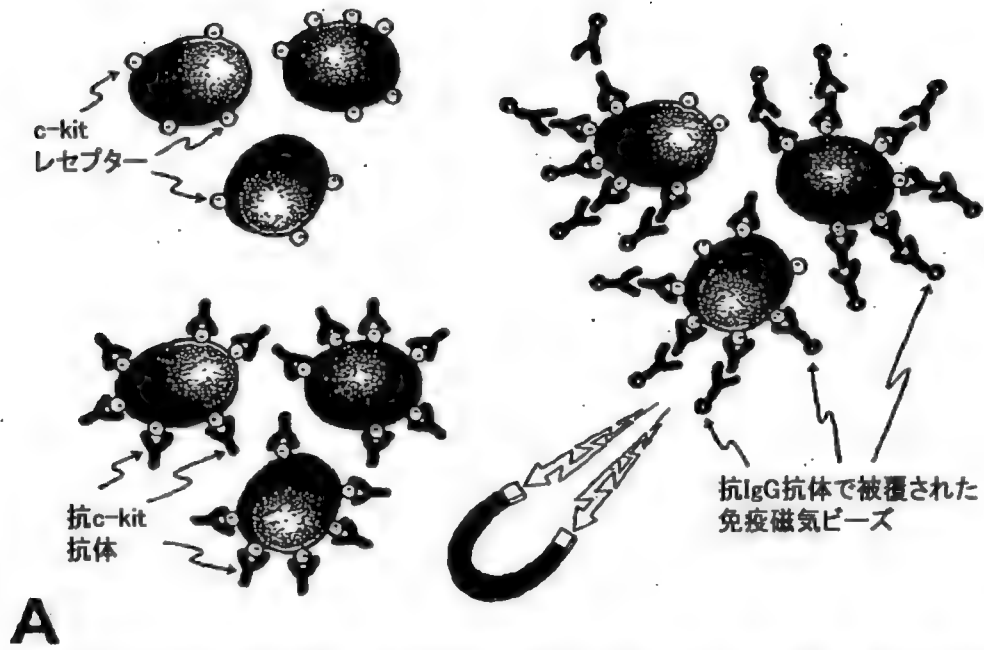
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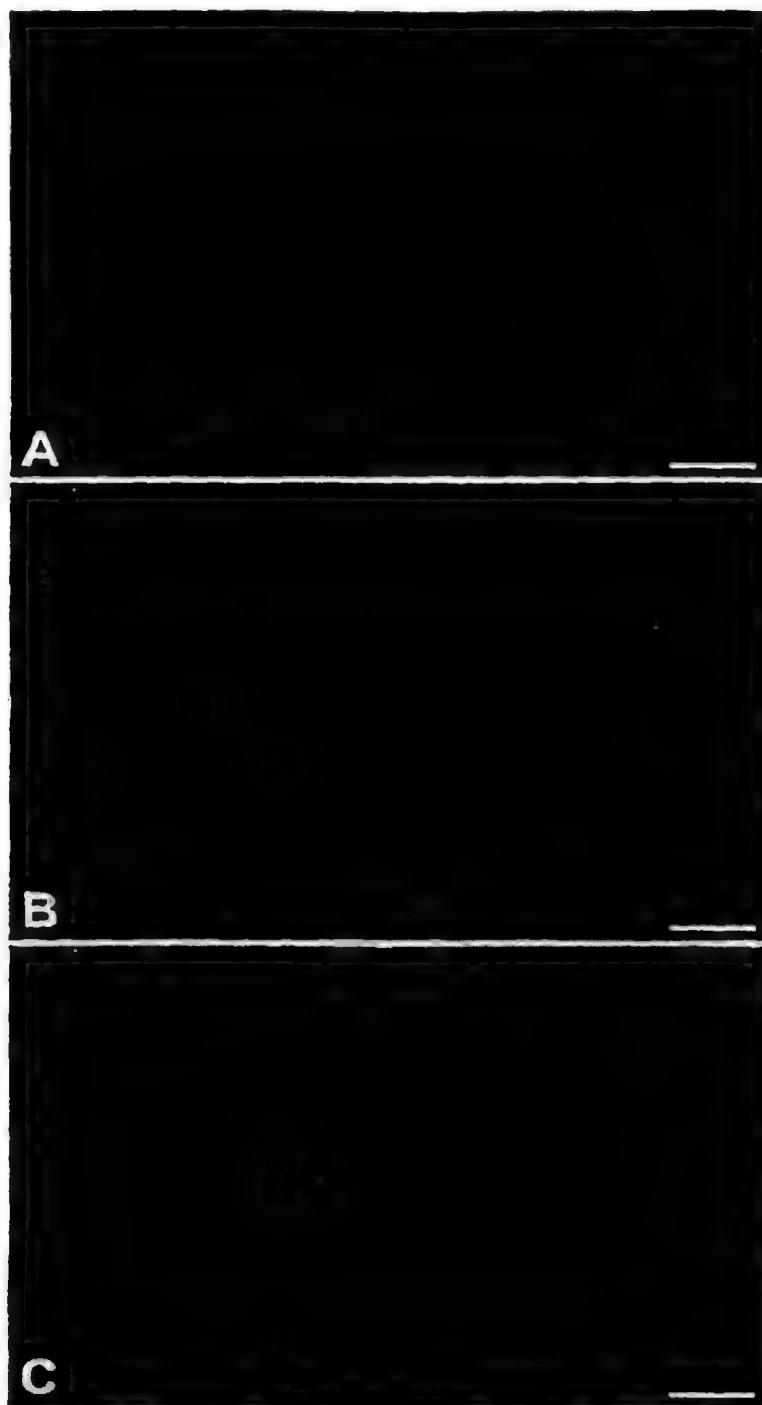
□ □ □ □ □ - □ □



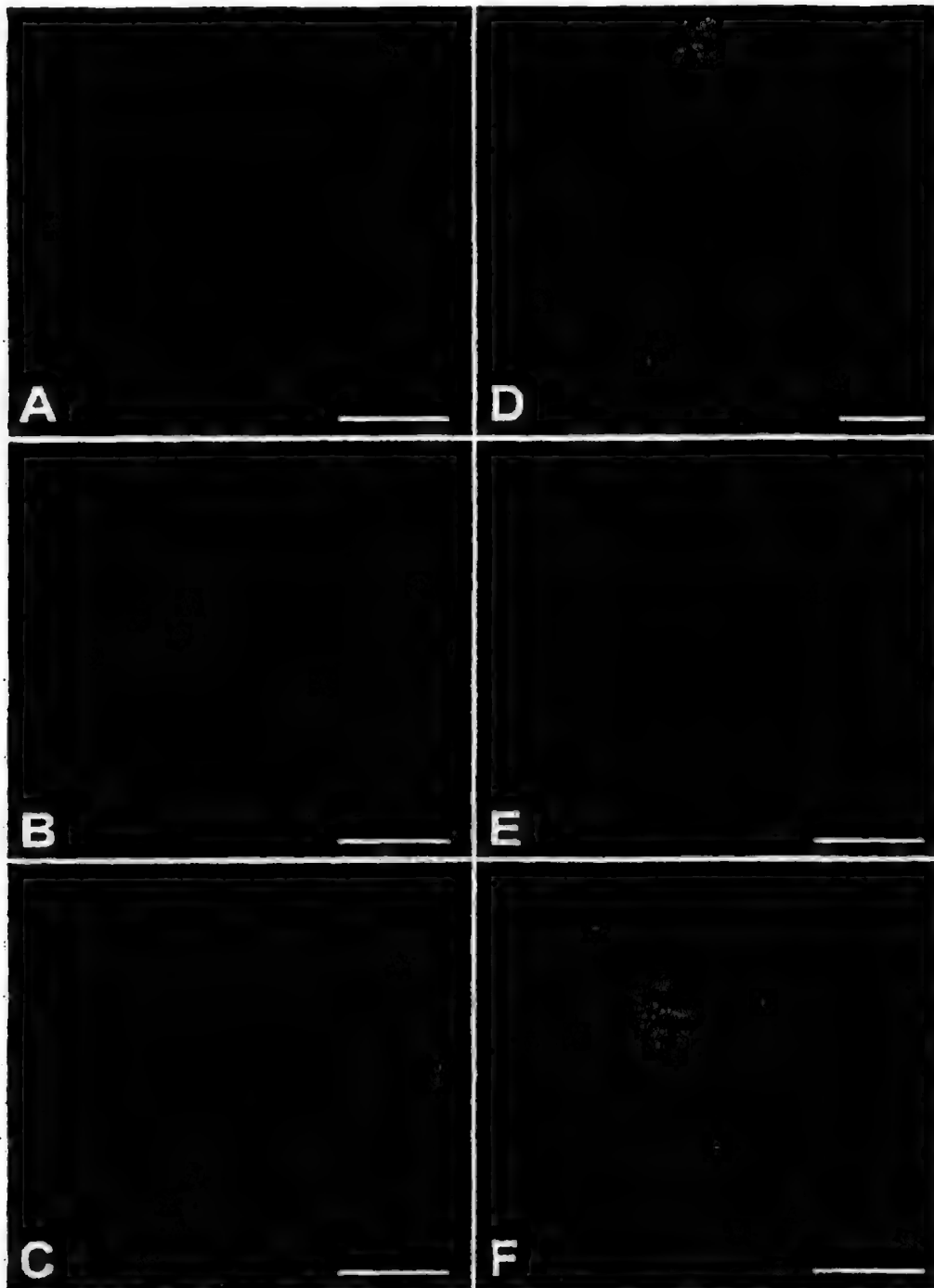


□ □ □ □ □ - □ □

# 心筋細胞分化の転写因子

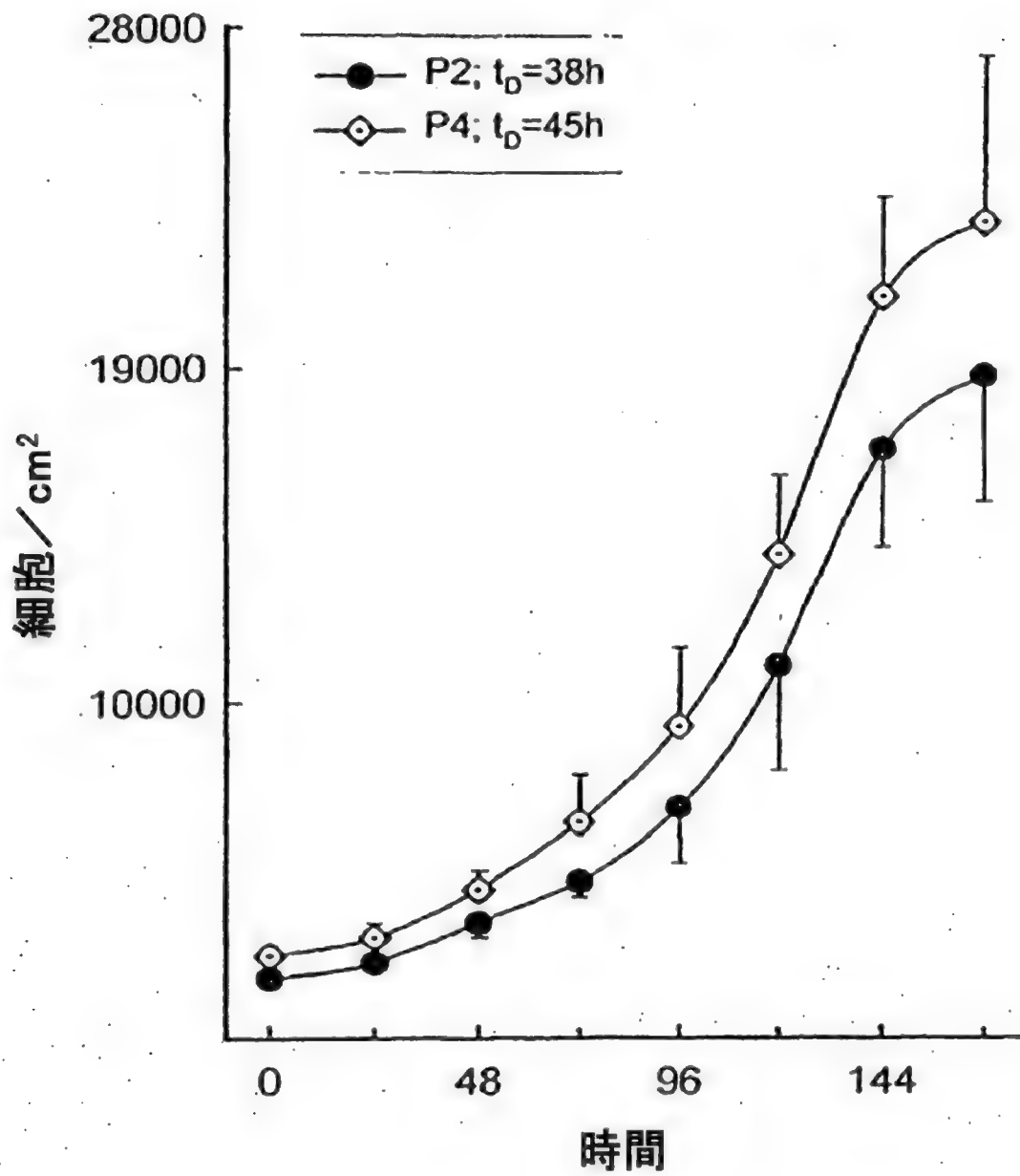


□ □ □ □ □ - □ □

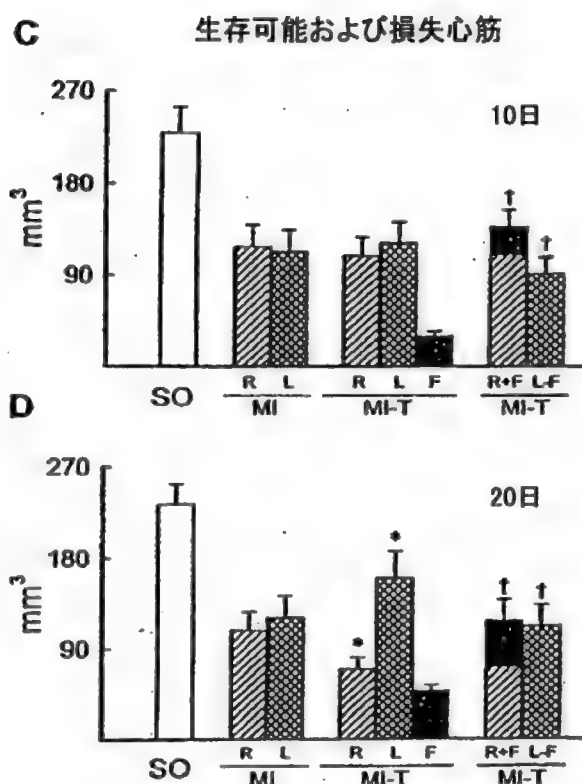
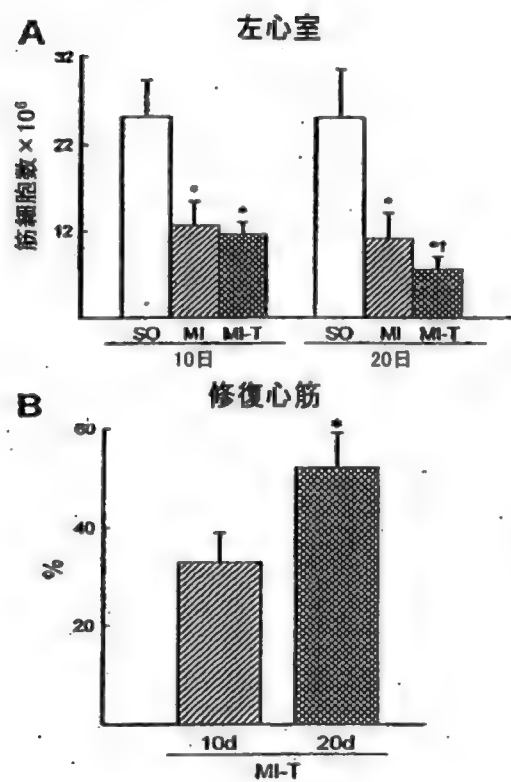
**c-kit<sup>POS</sup>細胞および骨格筋分化の転写因子**

□ □ □ □ □

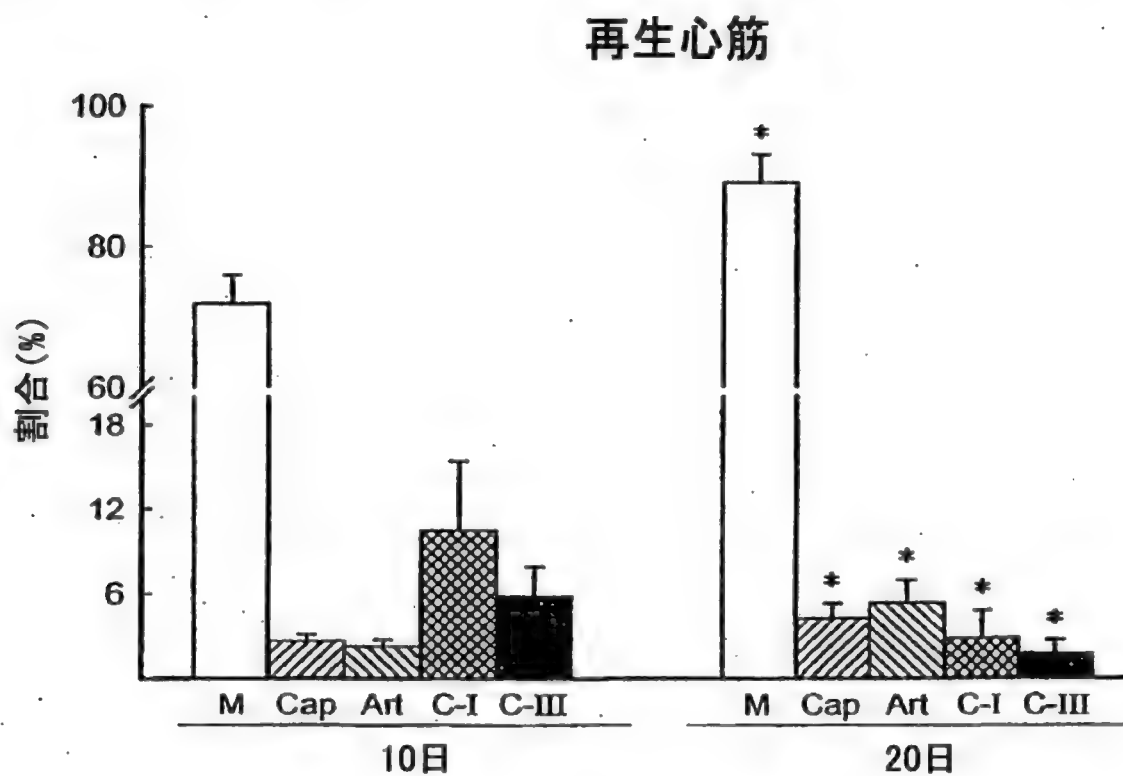
# c-kit<sup>POS</sup>由来細胞の成長



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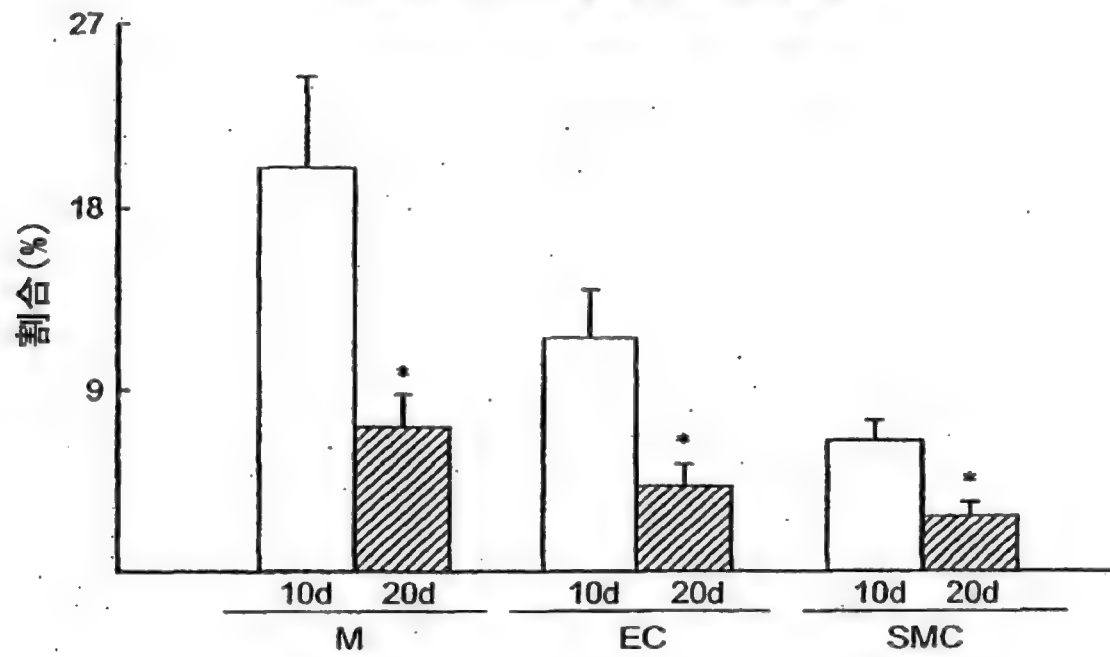


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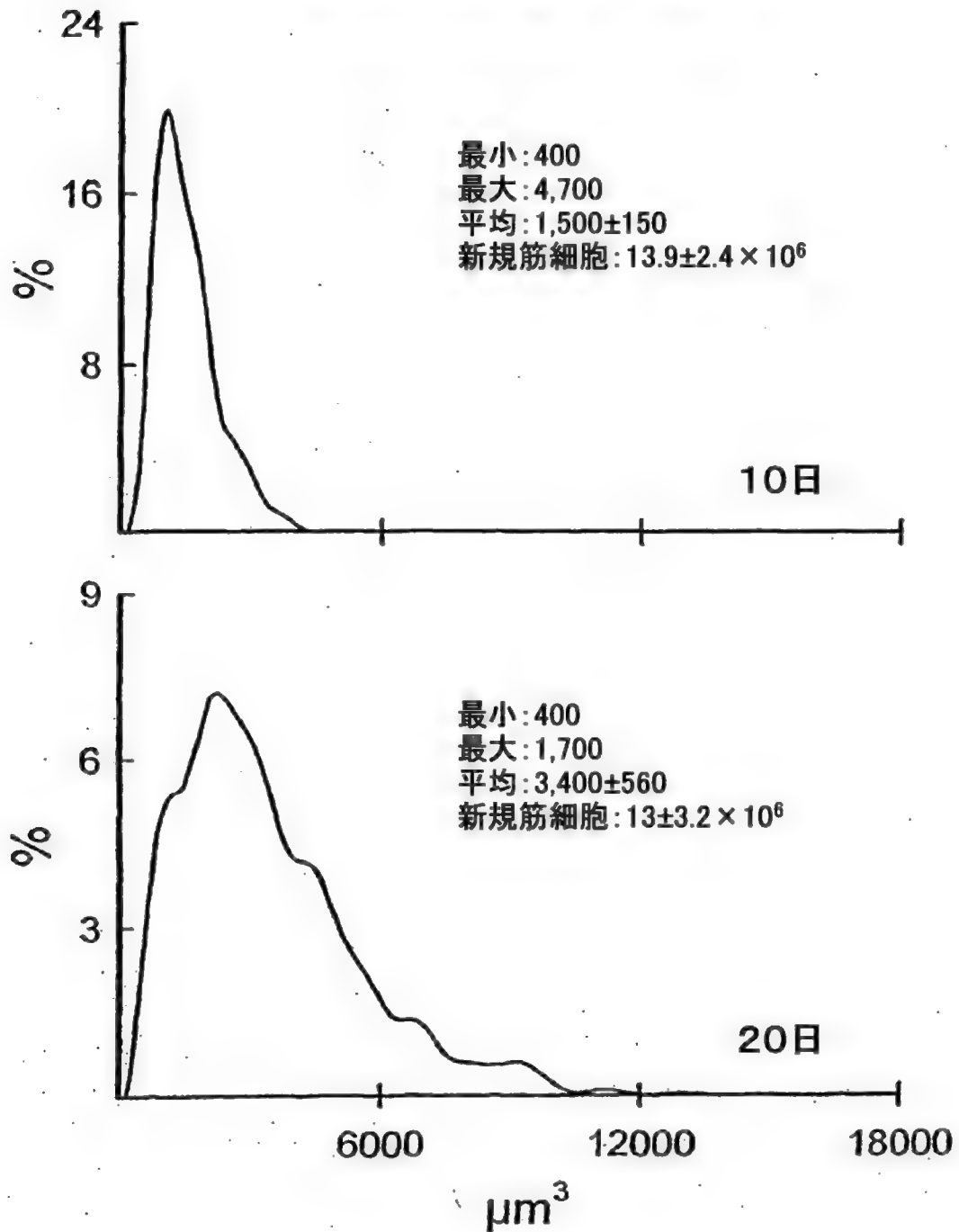
□ □ □ □ □

## Ki67によって標識された細胞

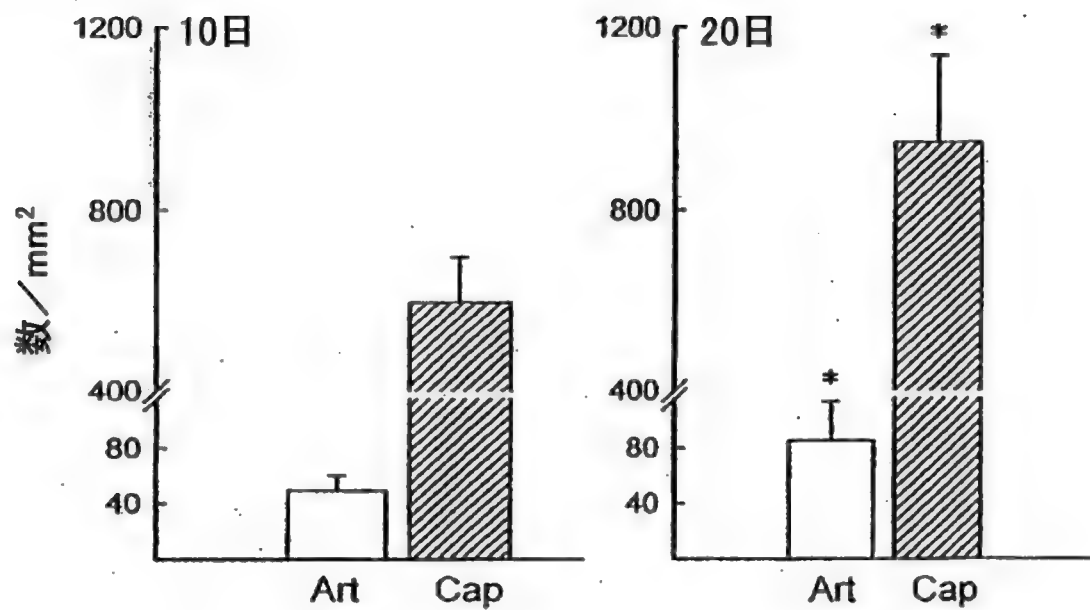


□ □ □ □ □

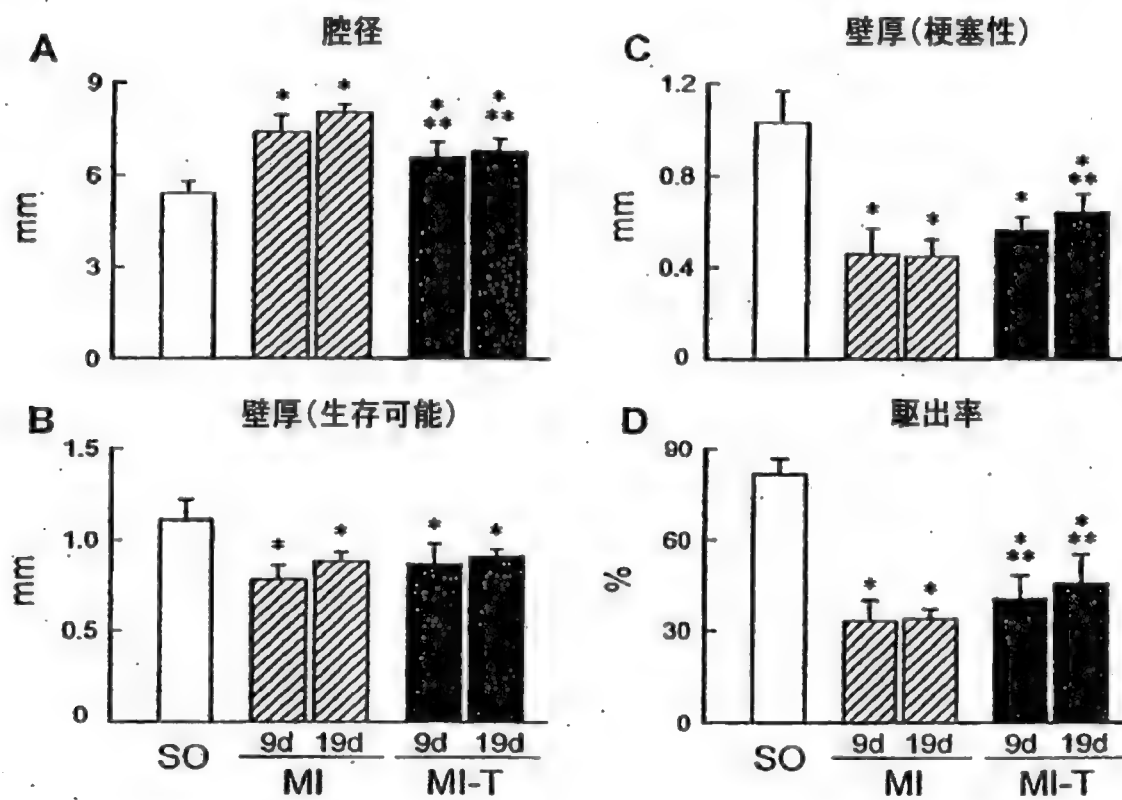
## 筋細胞の容積および数



□ □ □ □ □

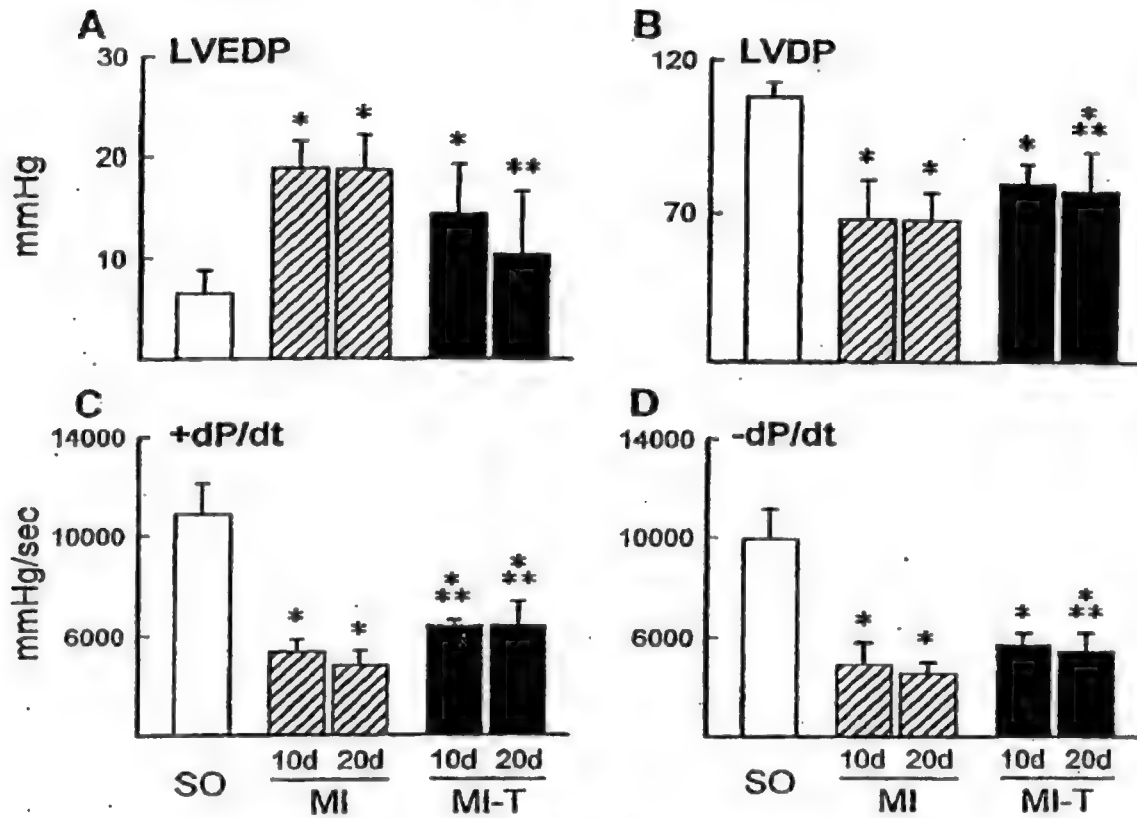


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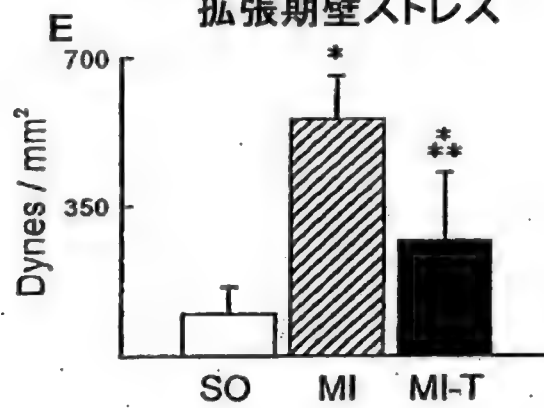


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## 左心室機能



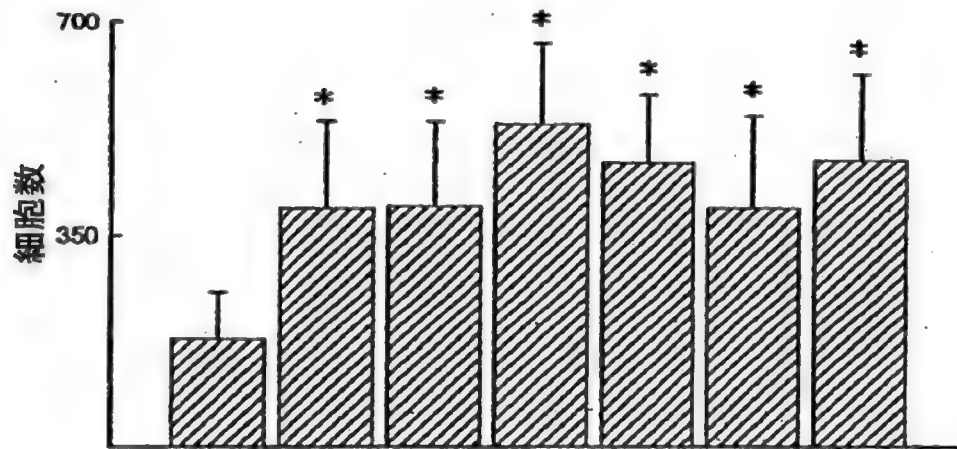
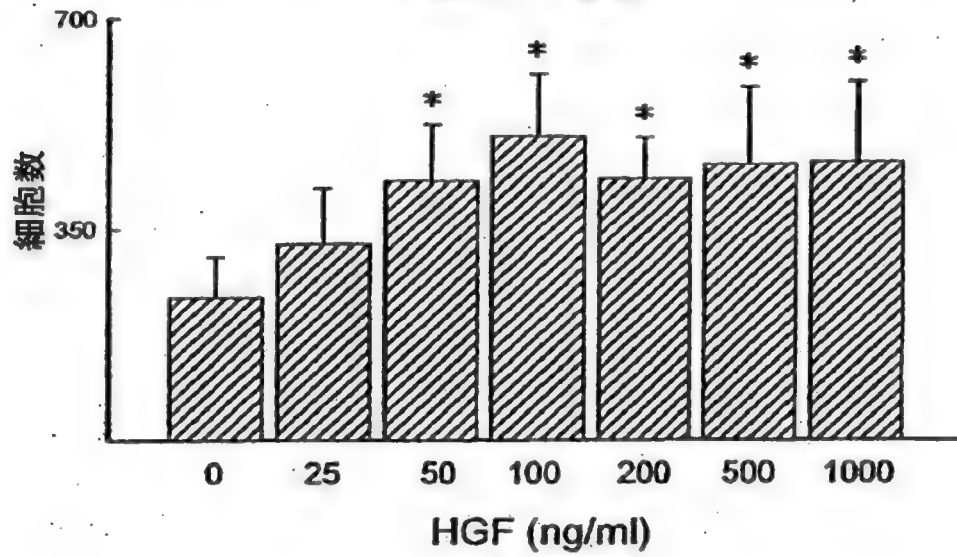
## 拡張期壁ストレス





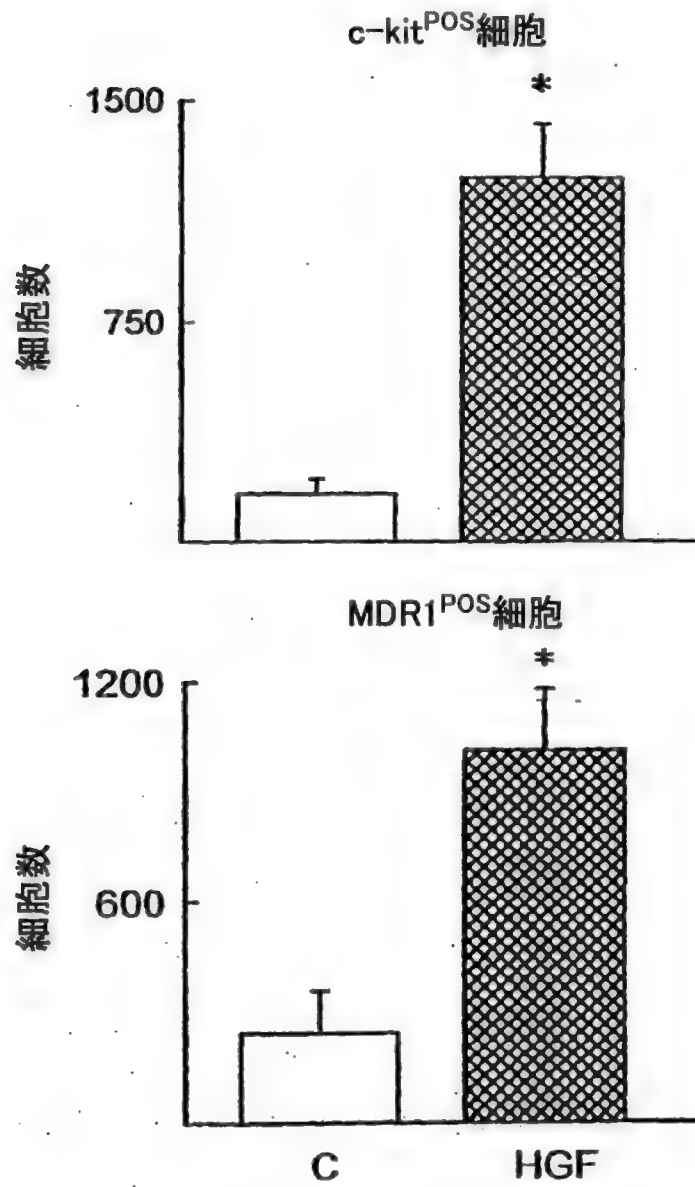
□ □ □ □ □

## 移動アッセイ

c-kit<sup>POS</sup>細胞MDR1<sup>POS</sup>細胞

□ □ □ □ □

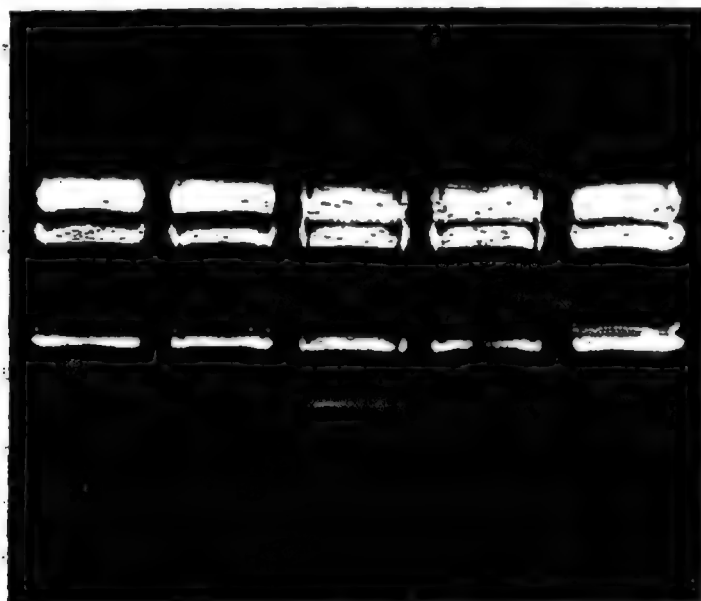
## 侵入アッセイ



□ □ □ □ □

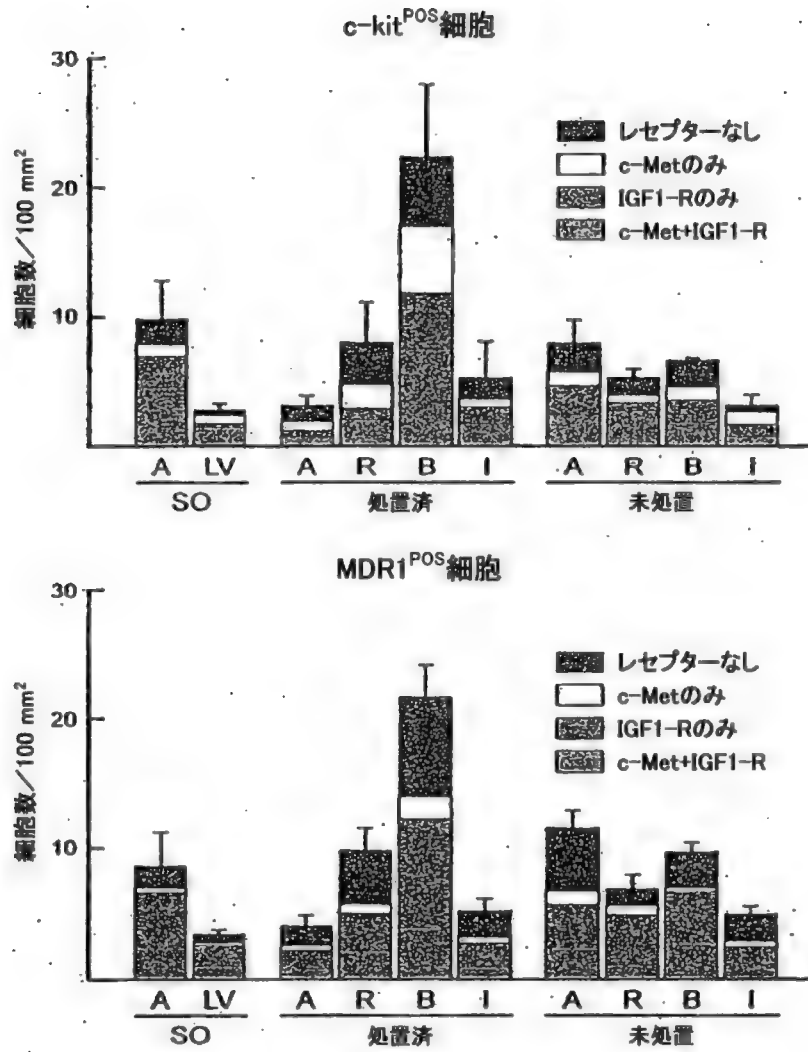
c-Met<sup>POS</sup>心臓細胞+

HGF (100 ng/ml)



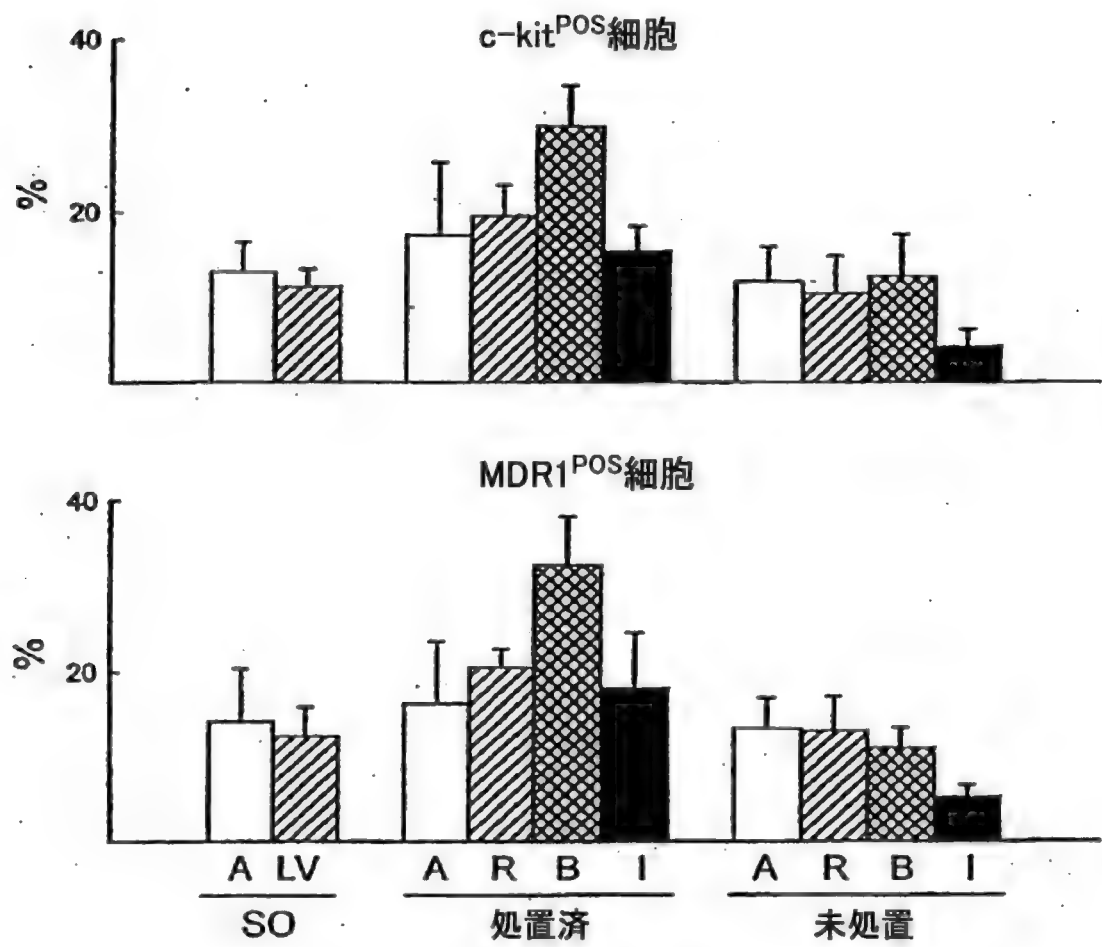
ゼラチン分解活性

□ □ □ □ □



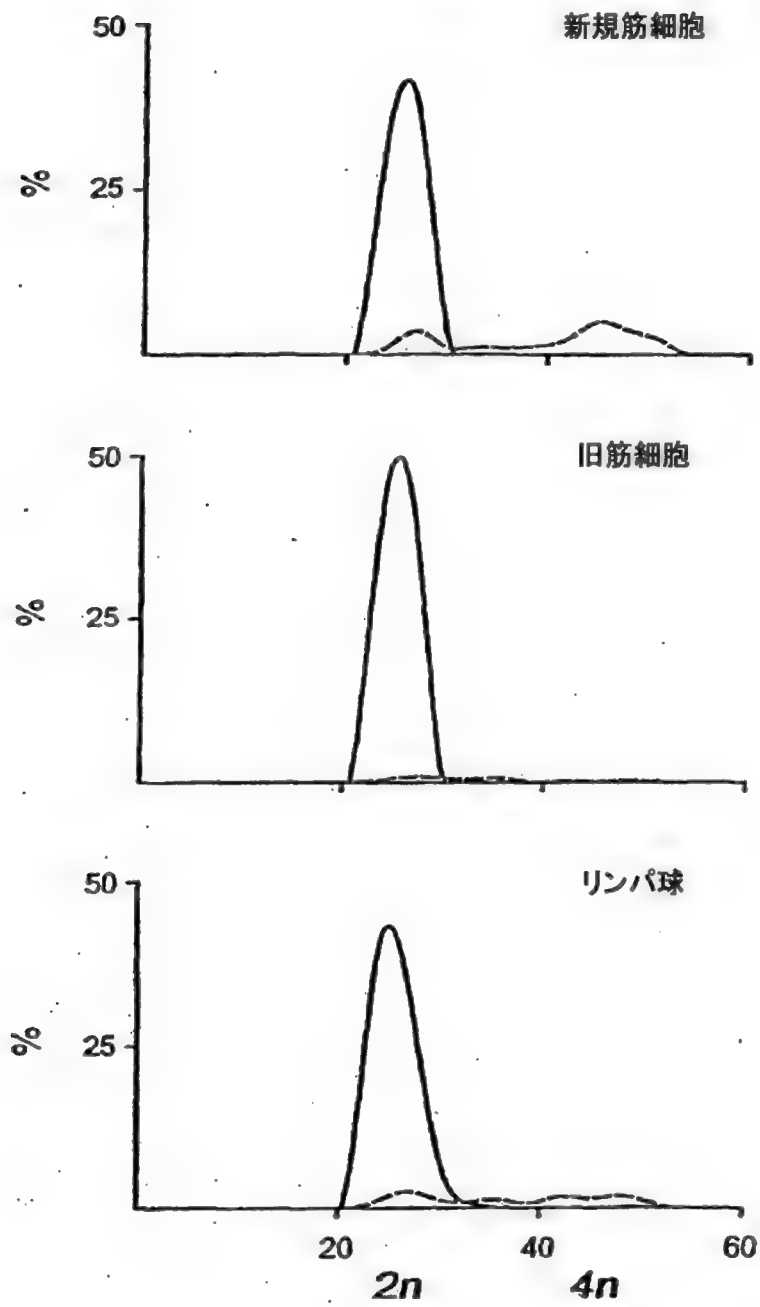
□ □ □ □ □

Ki67標識

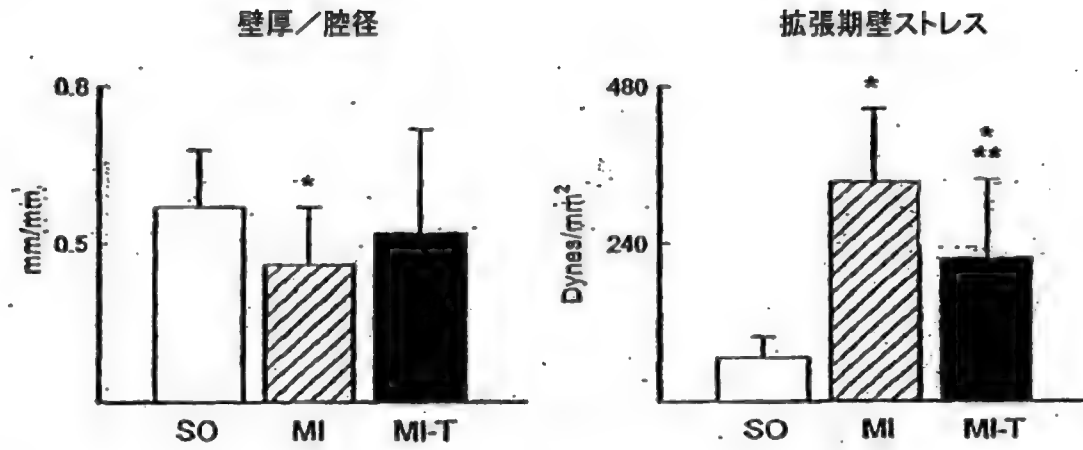


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## DNA含有量

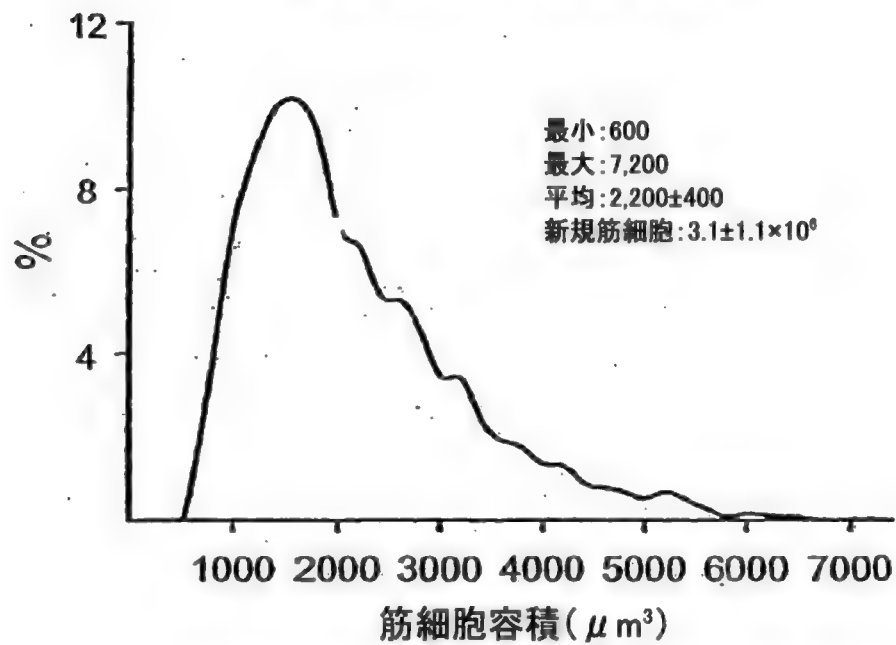


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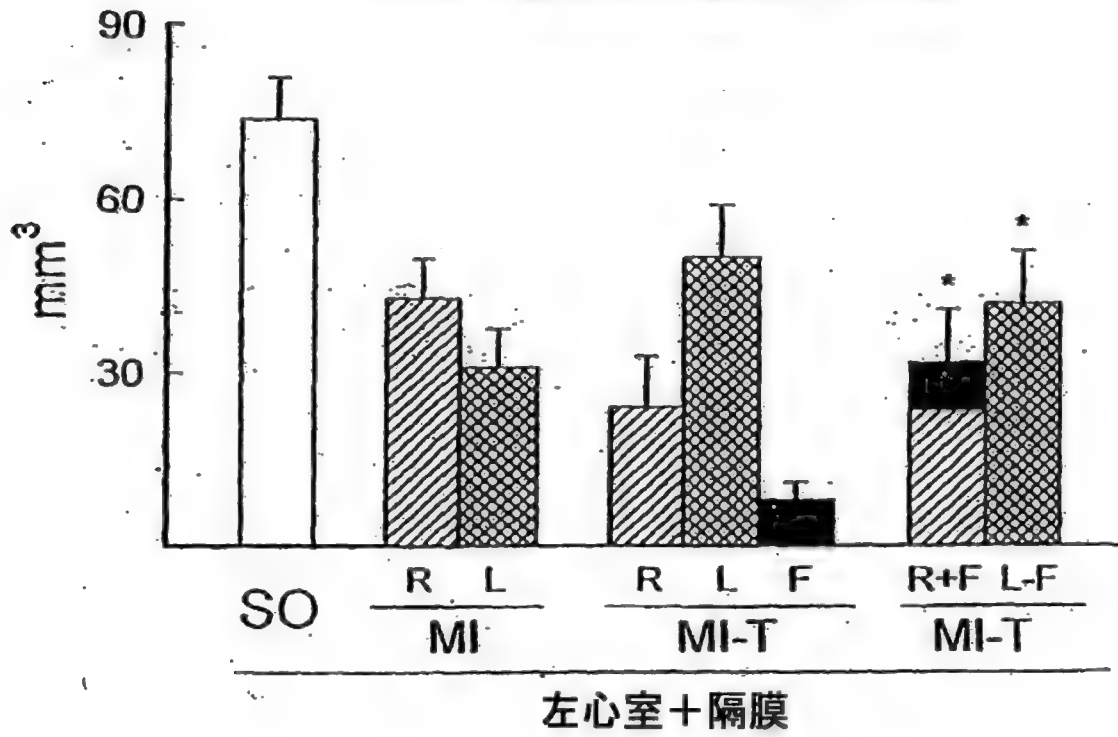
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## 筋細胞サイズの頻度分布



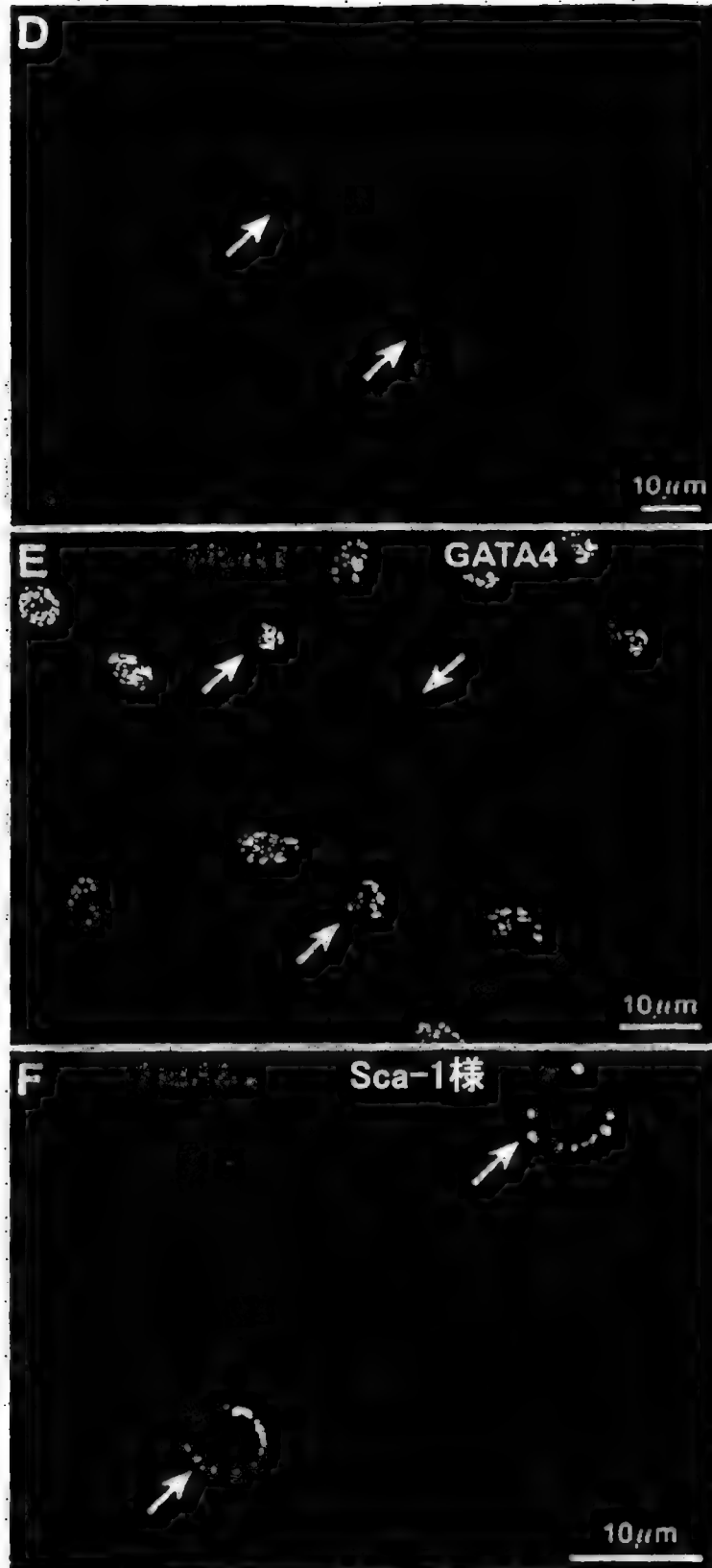
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## 生存可能および損失した心筋

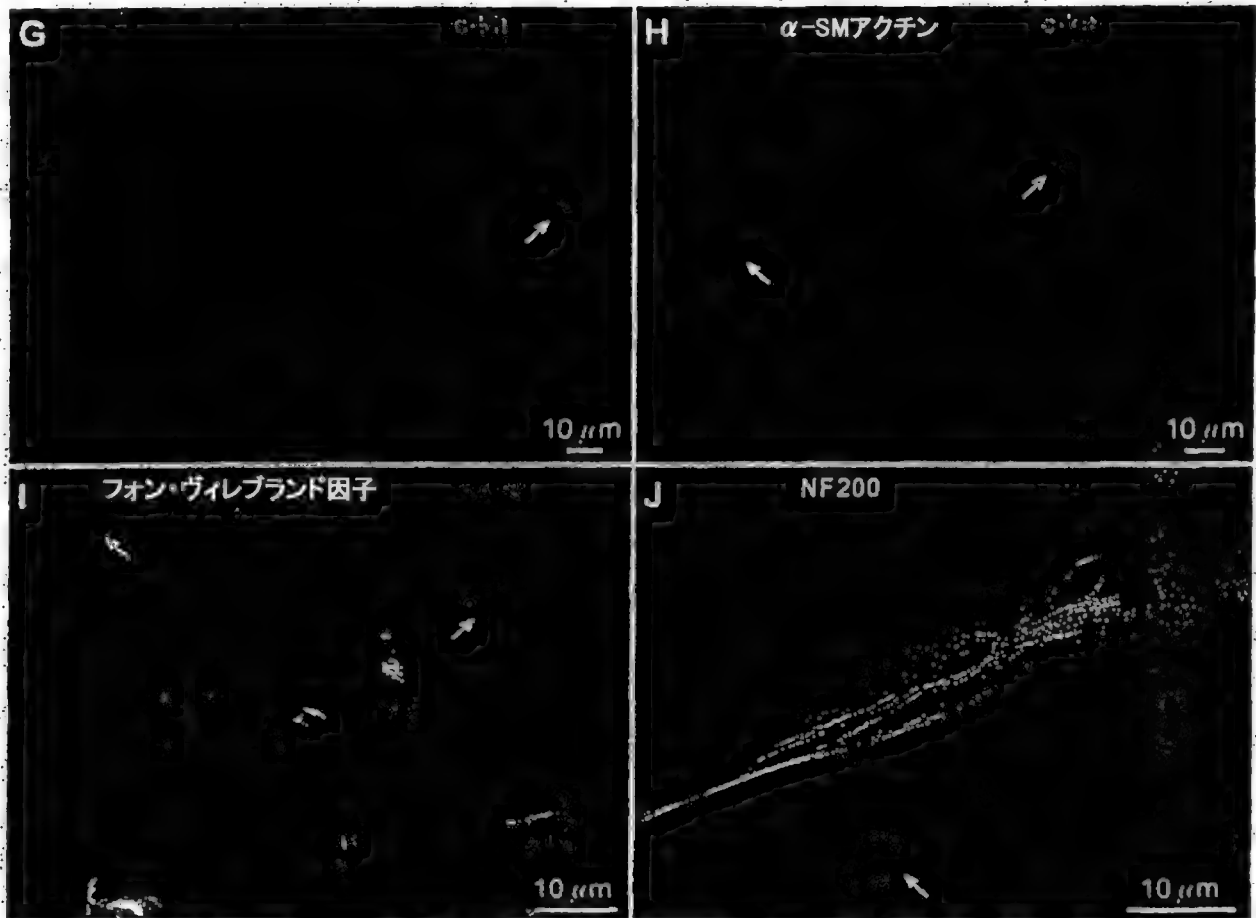




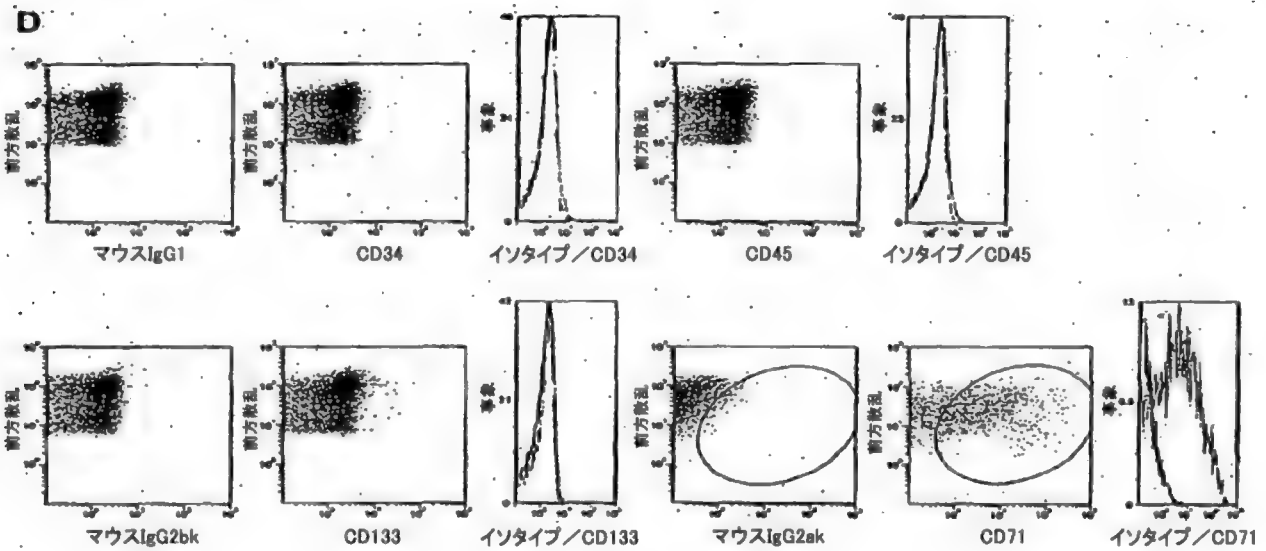
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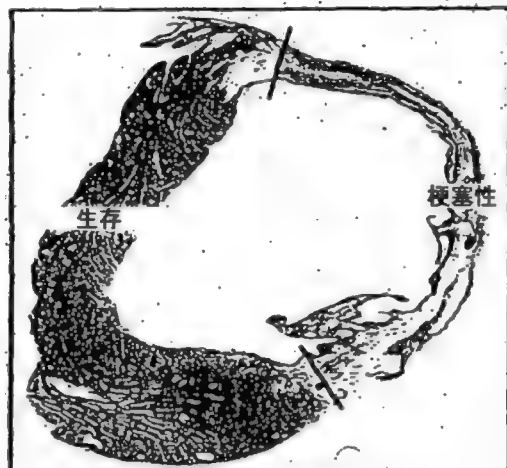
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□ □ □ □ □ □



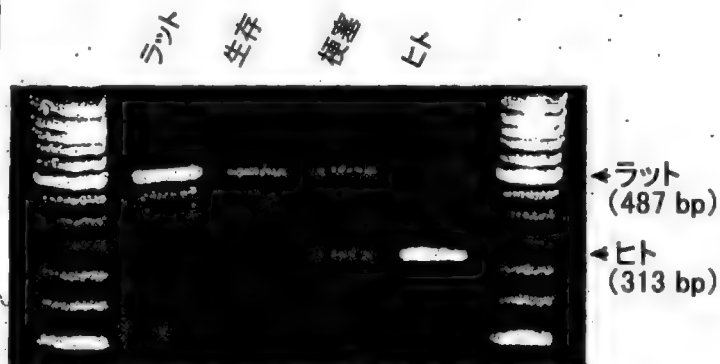
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**D**

H&amp;E

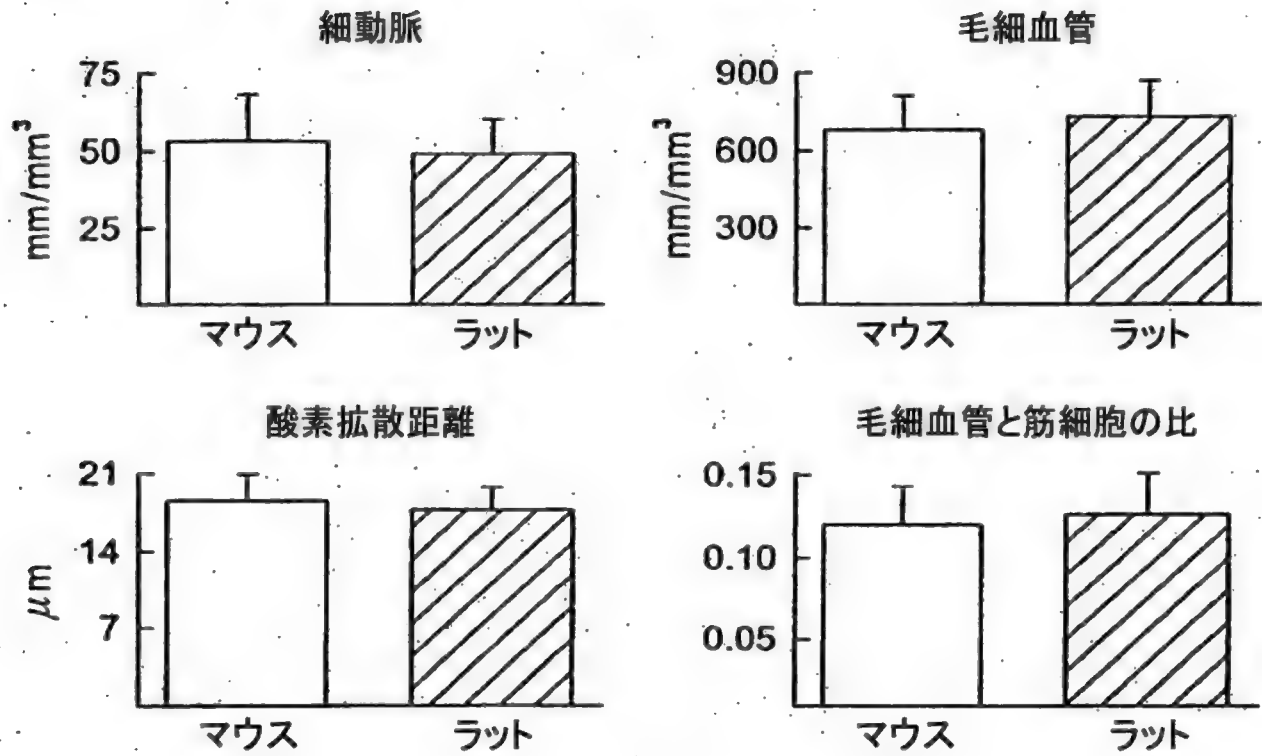


Alu DNA配列

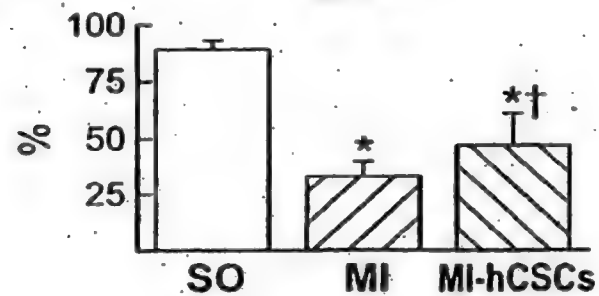


ミオシン軽鎖2v遺伝子

□ □ □ □ □

**G****血管形成**

□ □ □ □ □

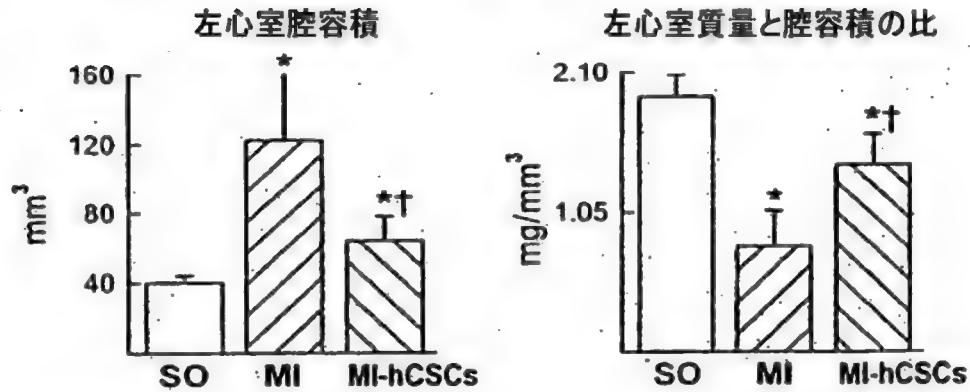
**D****駆出率**

□ □ □ □ □ □

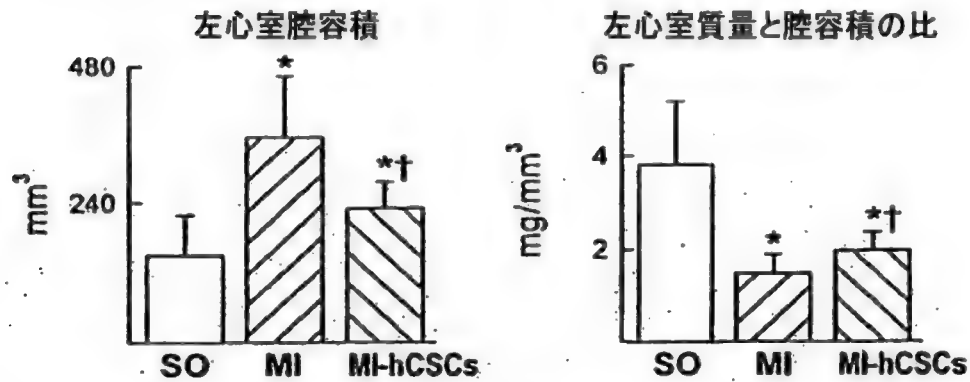
**E**

## 左心室の解剖分析

マウス



ラット

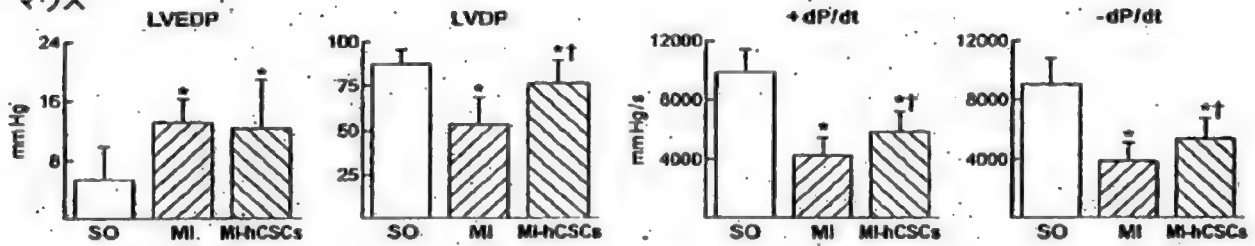


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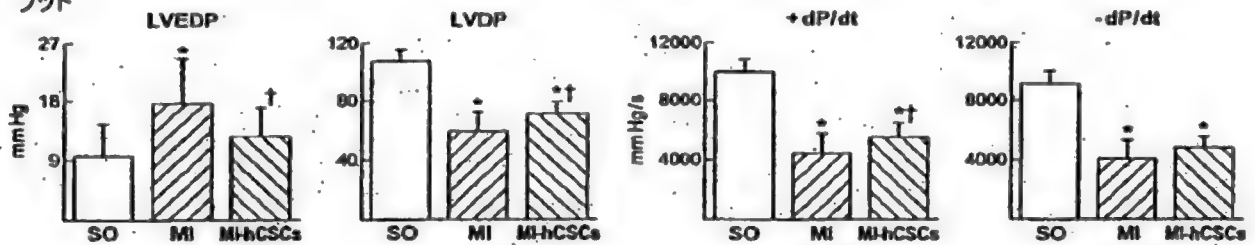
**F**

## 心室機能

マウス

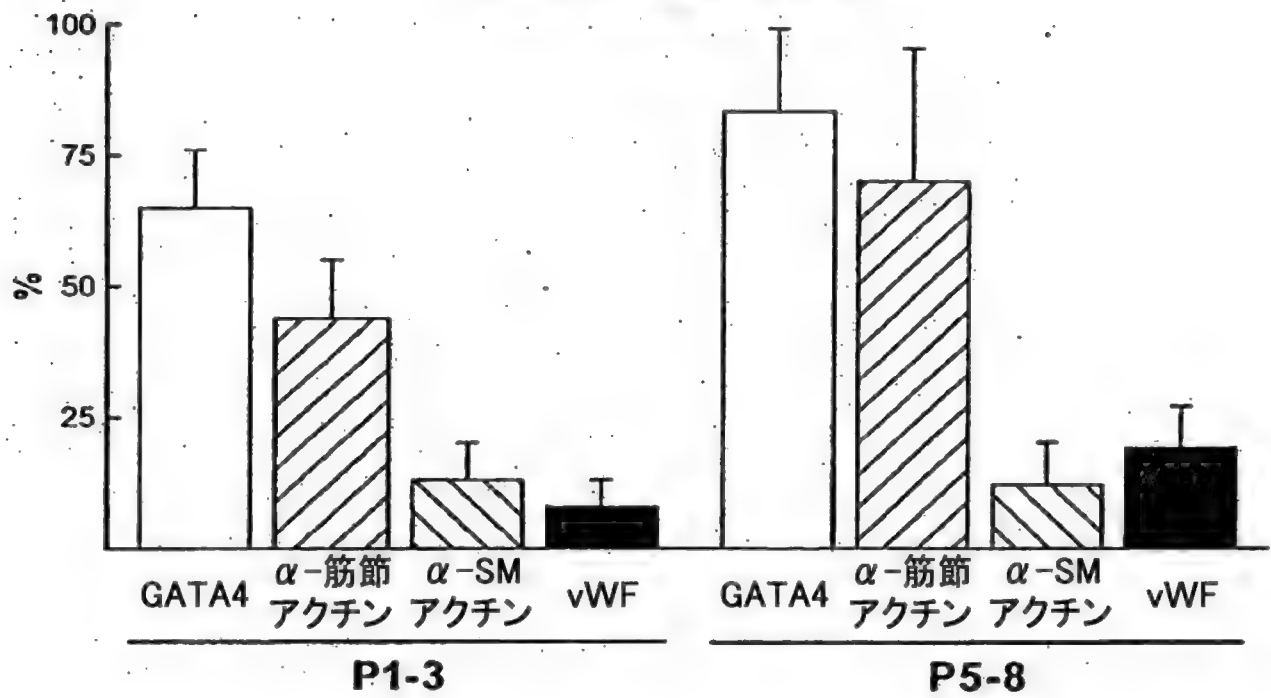


ラット

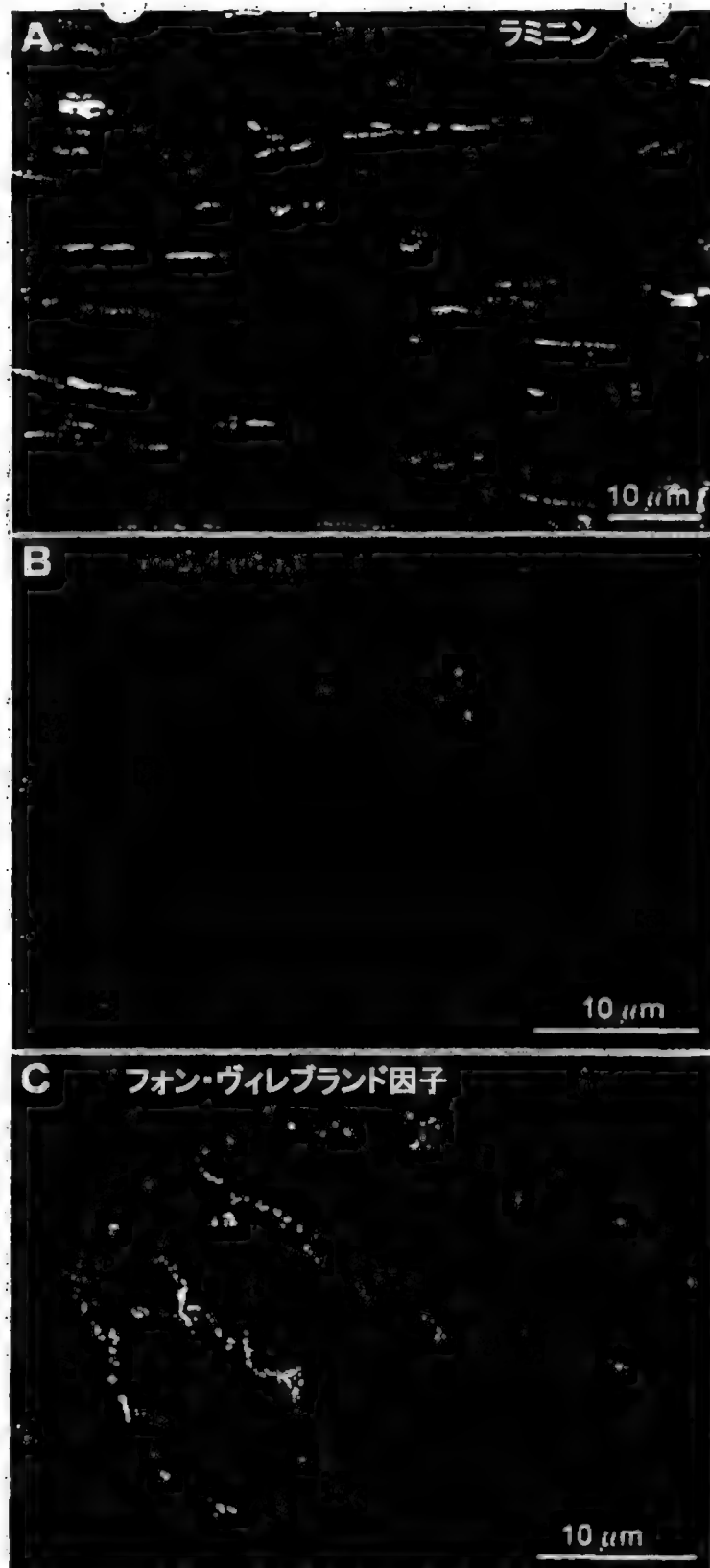


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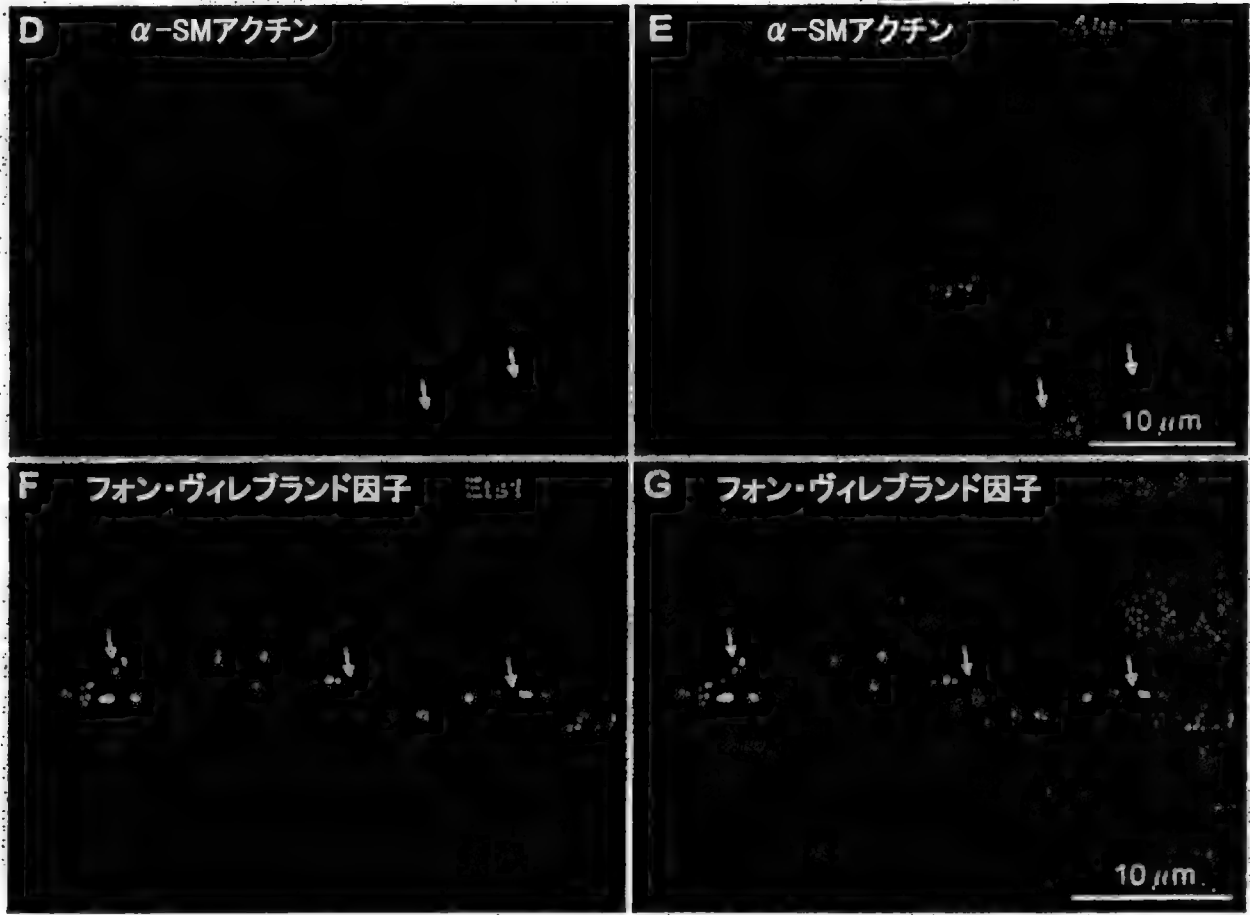
## c-kitPOS細胞の分化



□ □ □ □ □ - □ □



□ □ □ □ □ - □ □



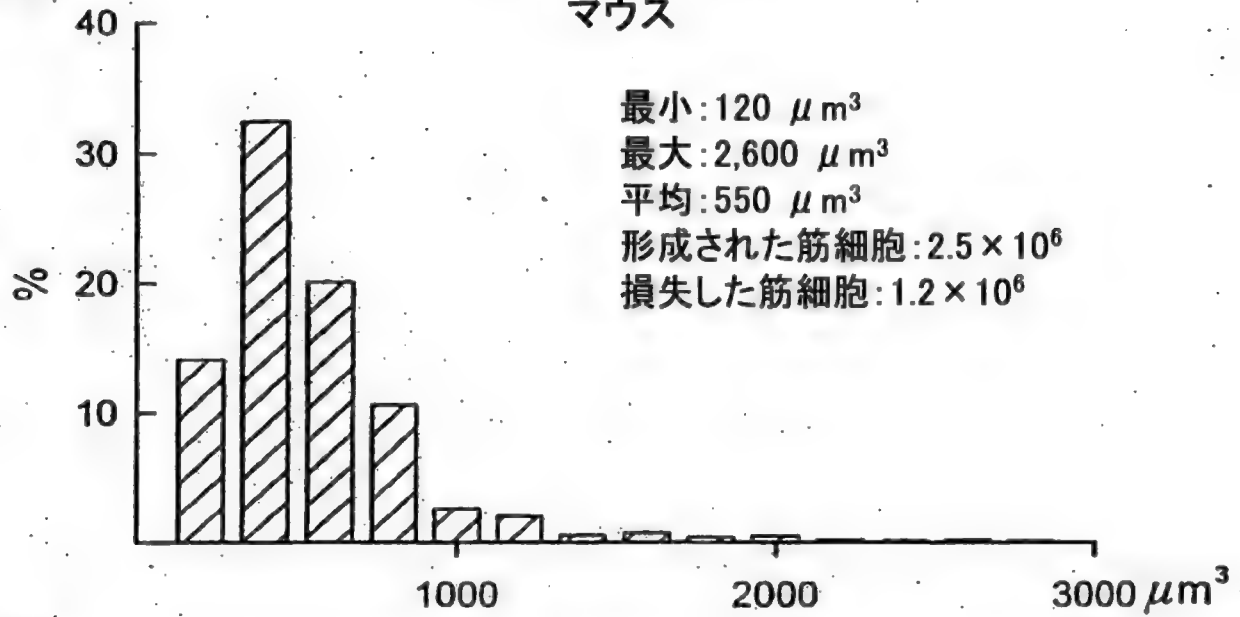


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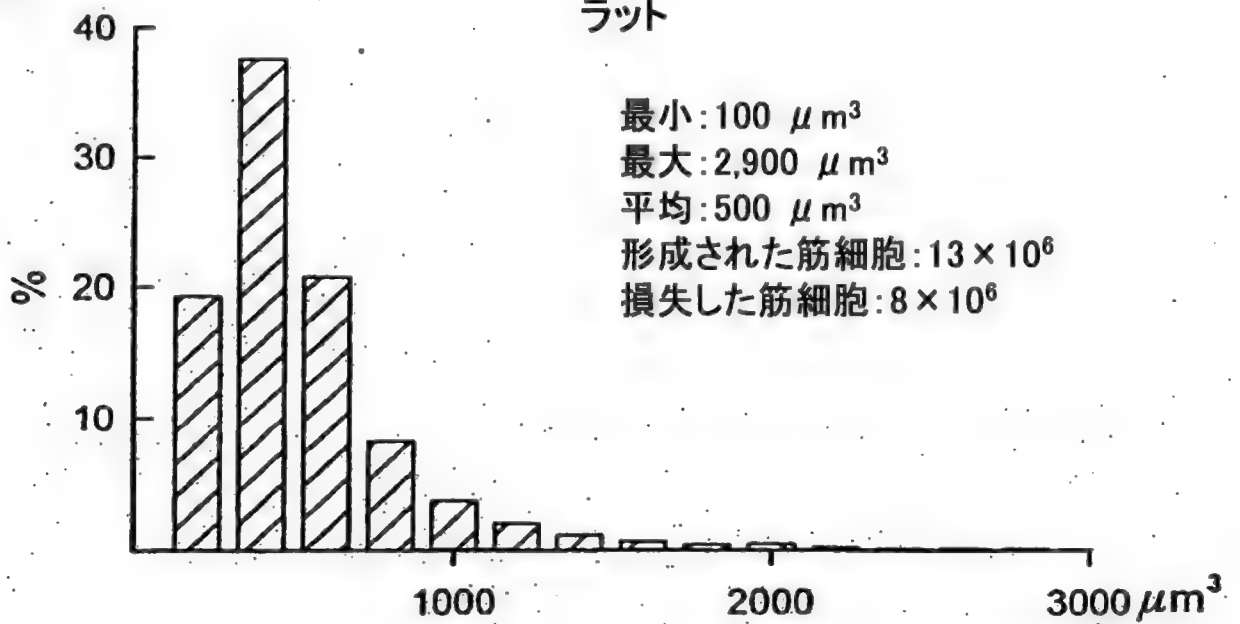
## ヒト筋細胞の容積

**A**

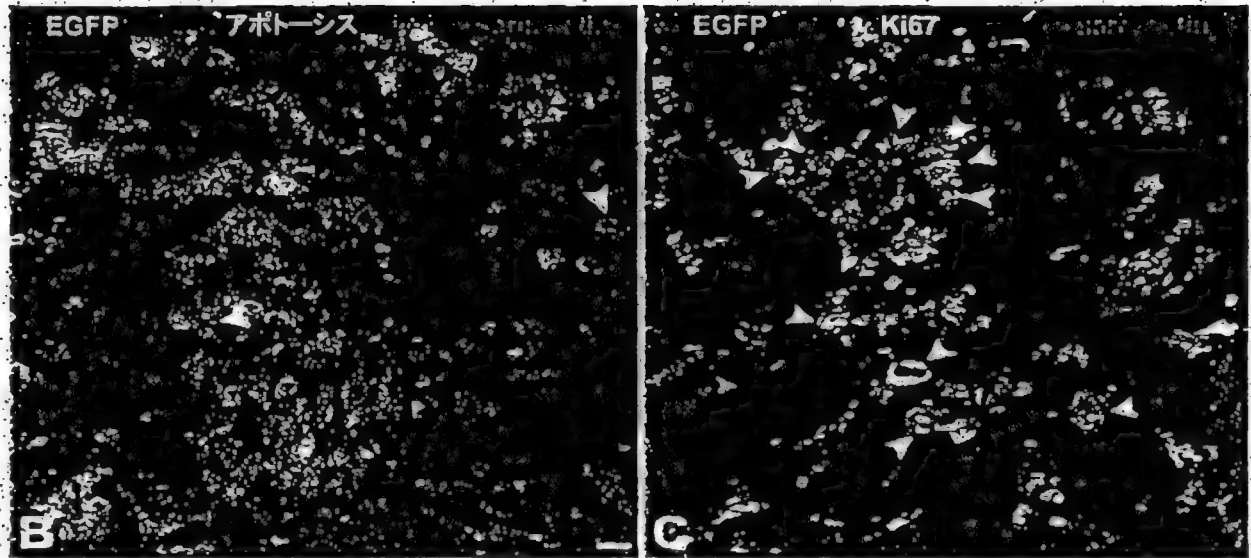
マウス

**B**

ラット

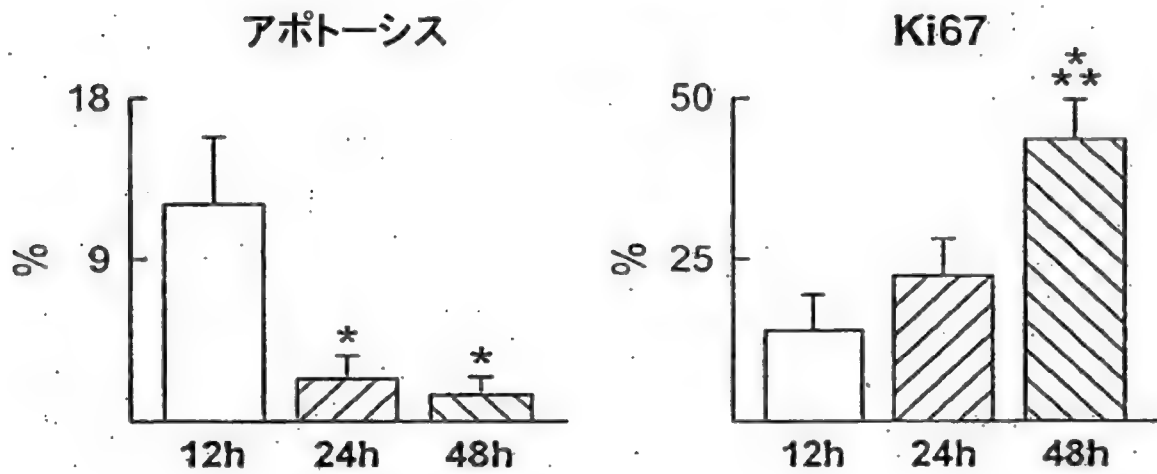


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## 活性化CSC

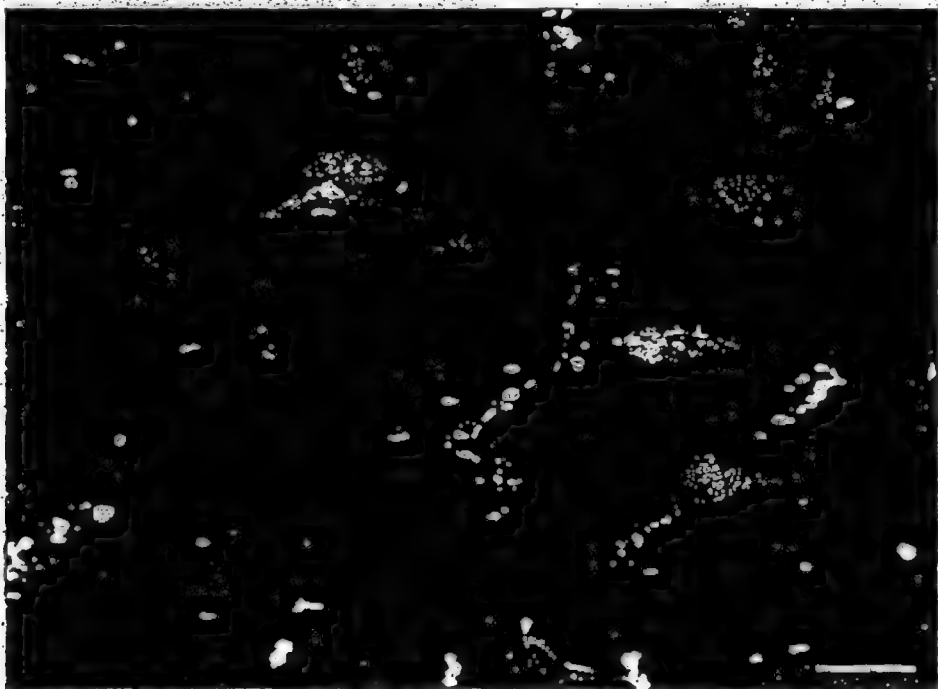


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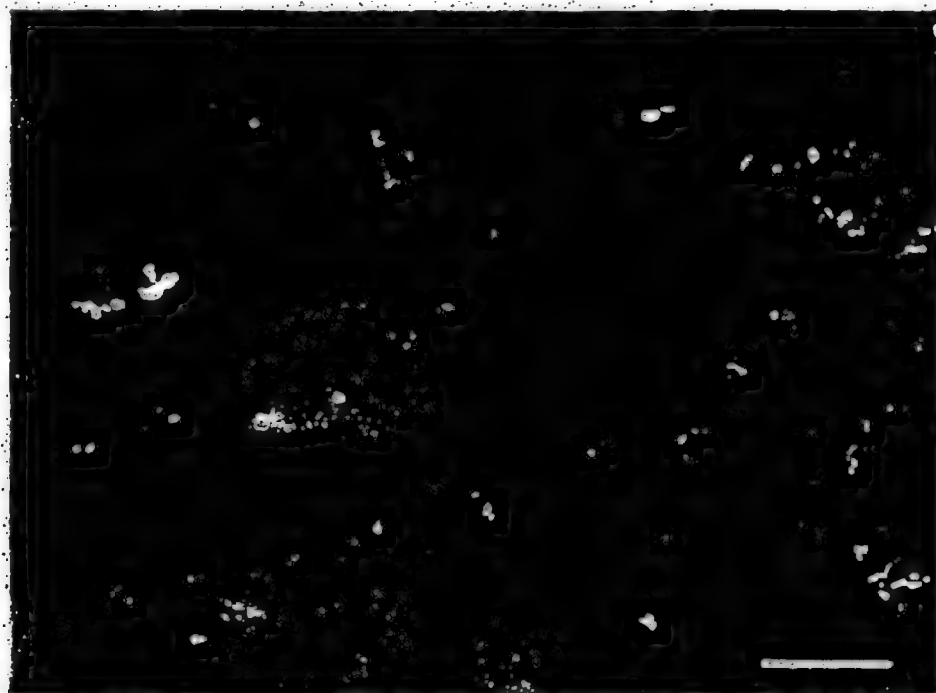
左パネル

□ □ □ □ □ - □ □



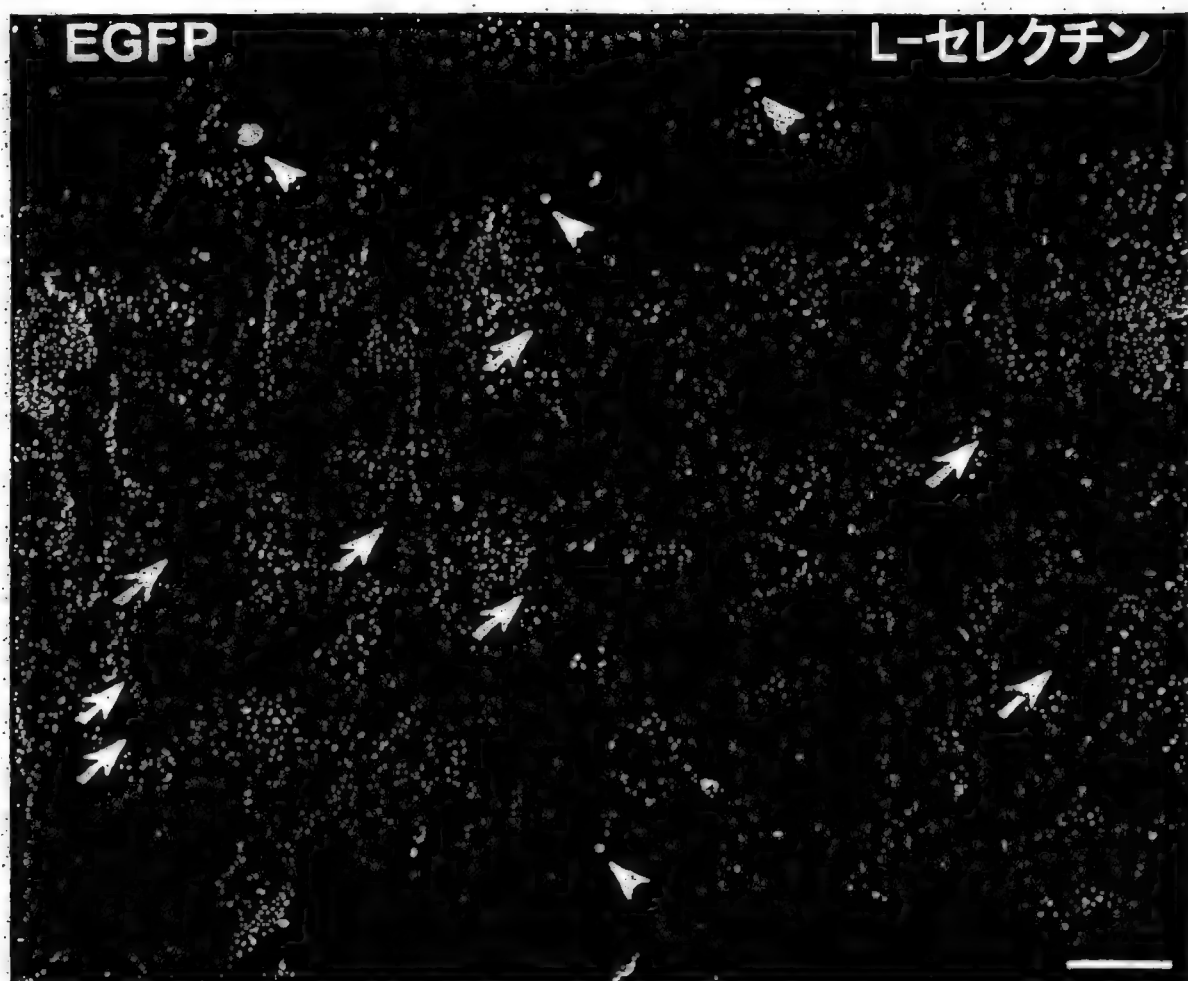
中央パネル

□ □ □ □ □ - □ □



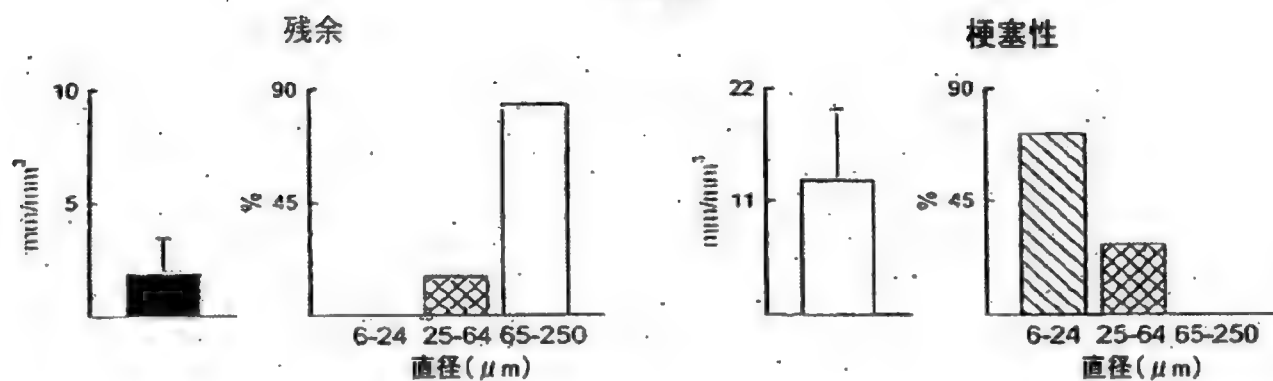
右パネル

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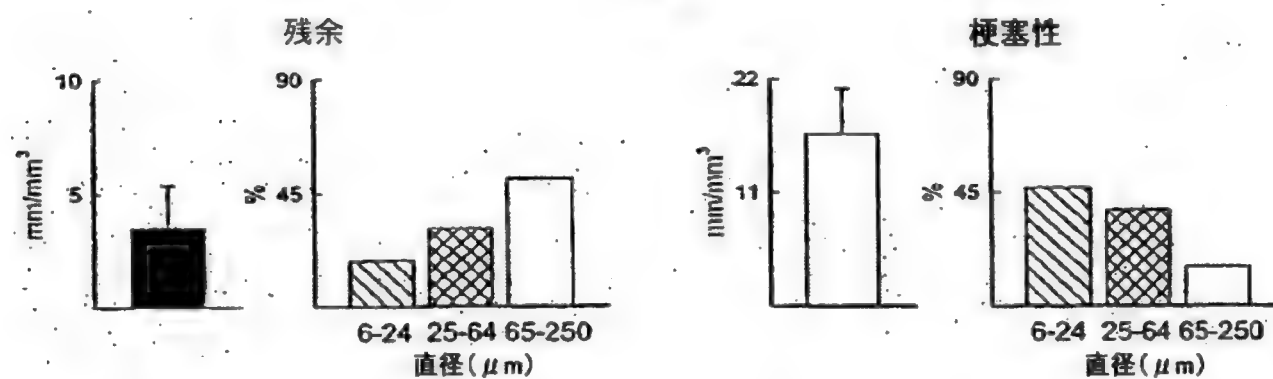


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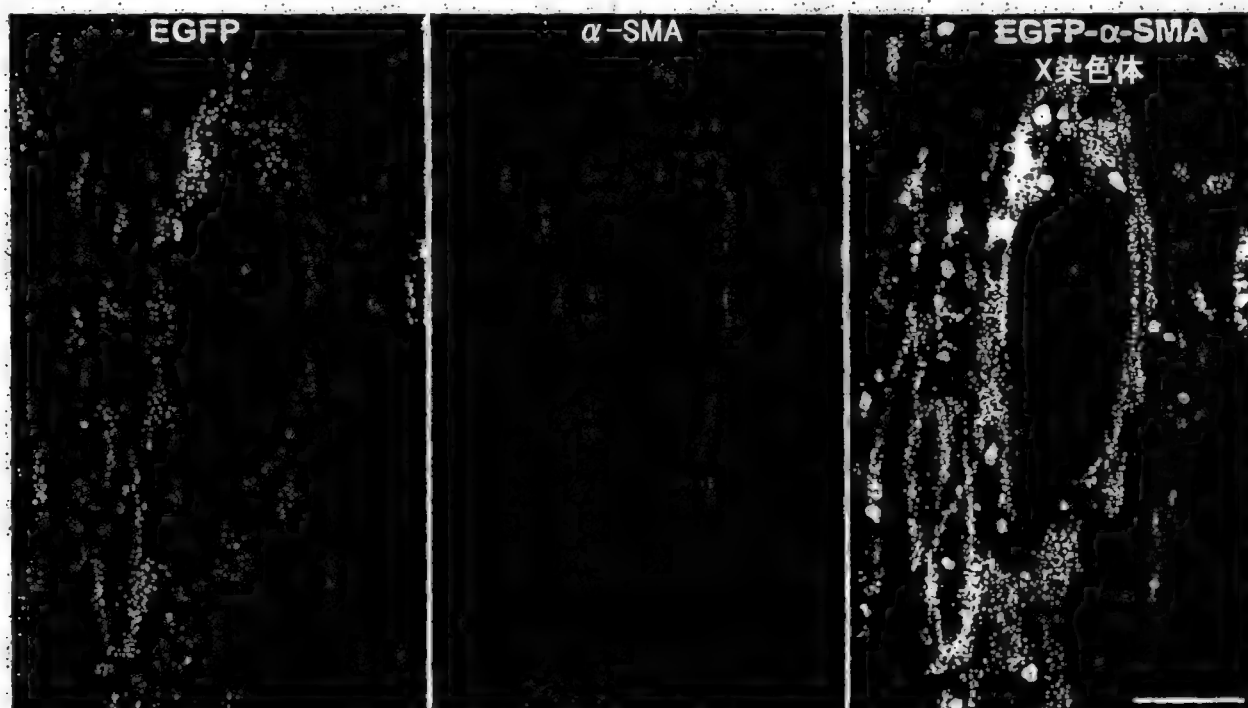
## 2週間



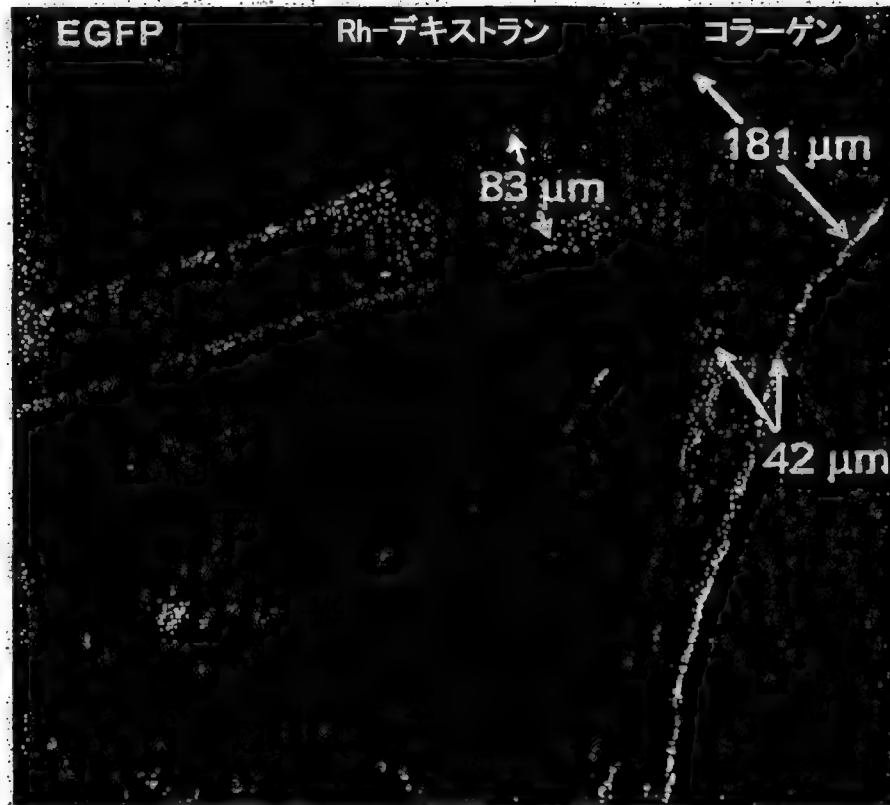
## 1ヶ月



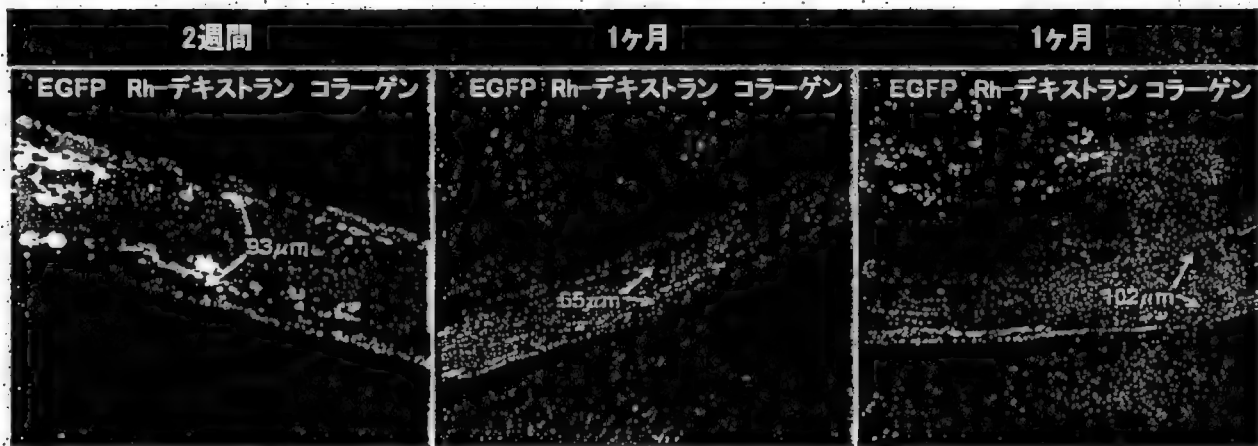
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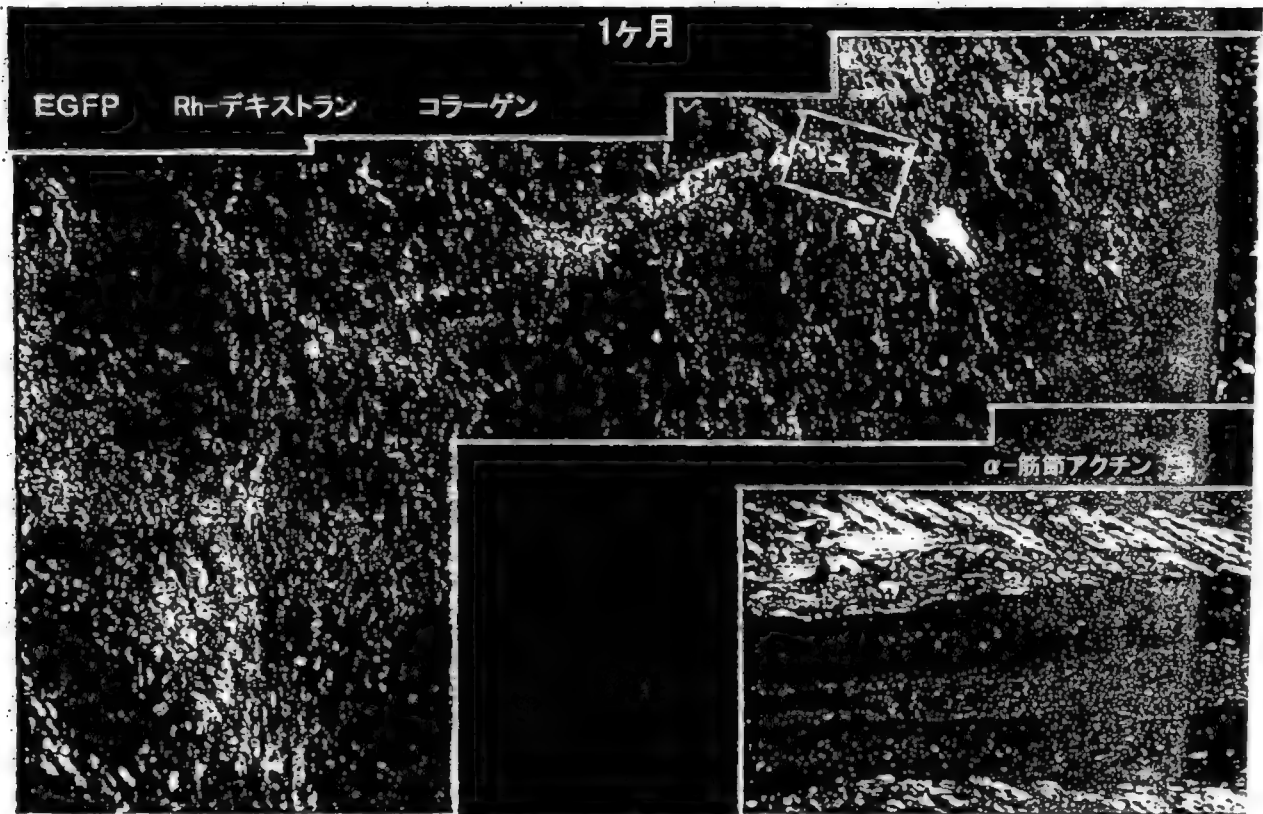


B

C

D

□ □ □ □ □ □



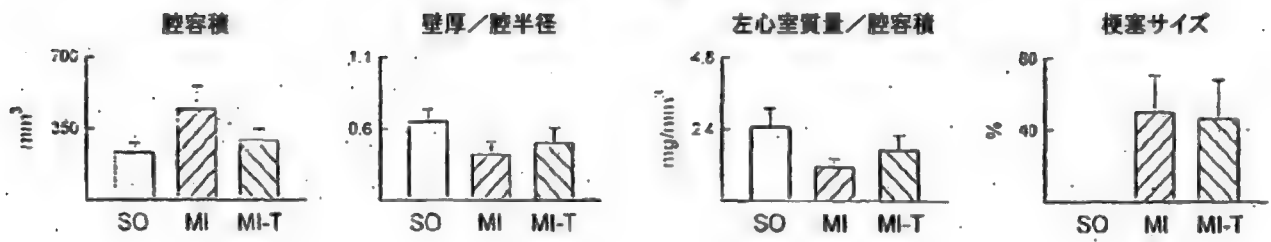
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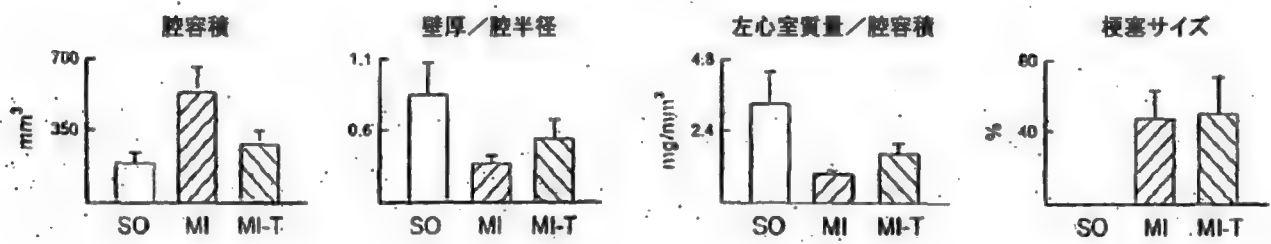
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## 心室解剖分析

2週間



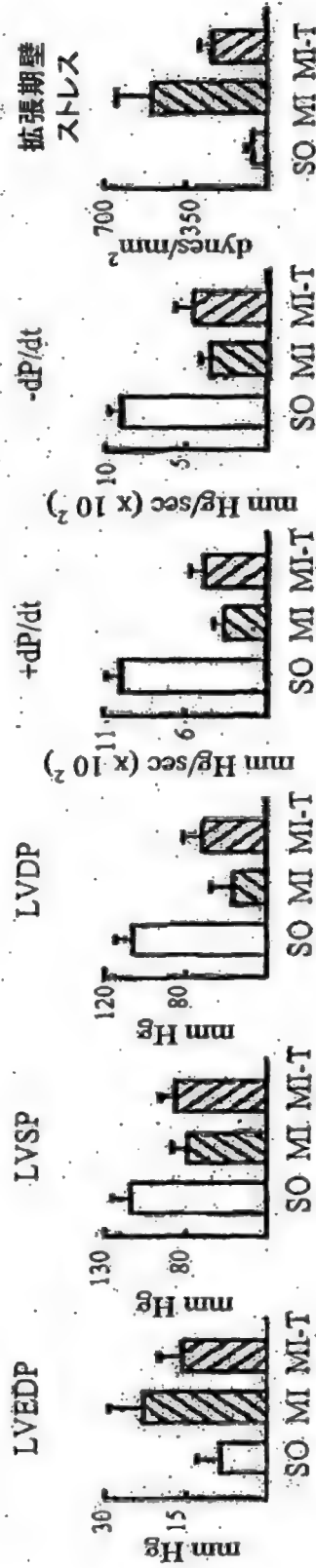
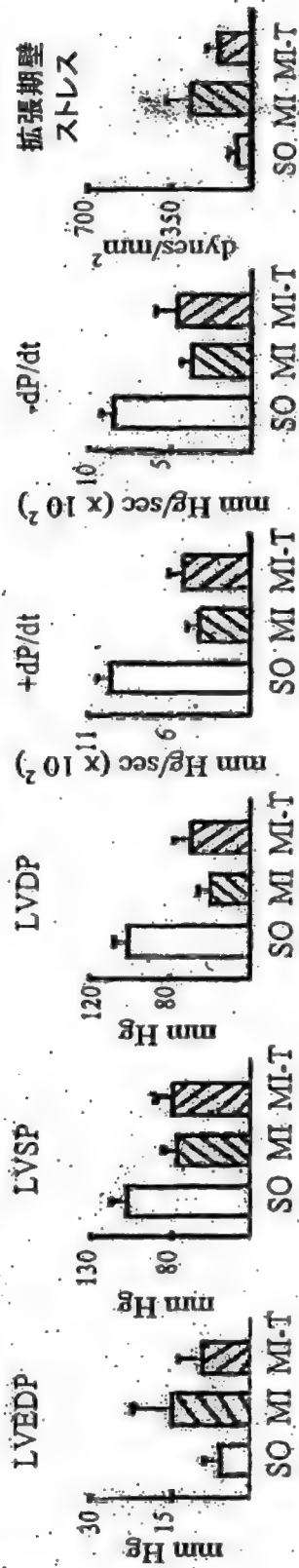
1ヶ月



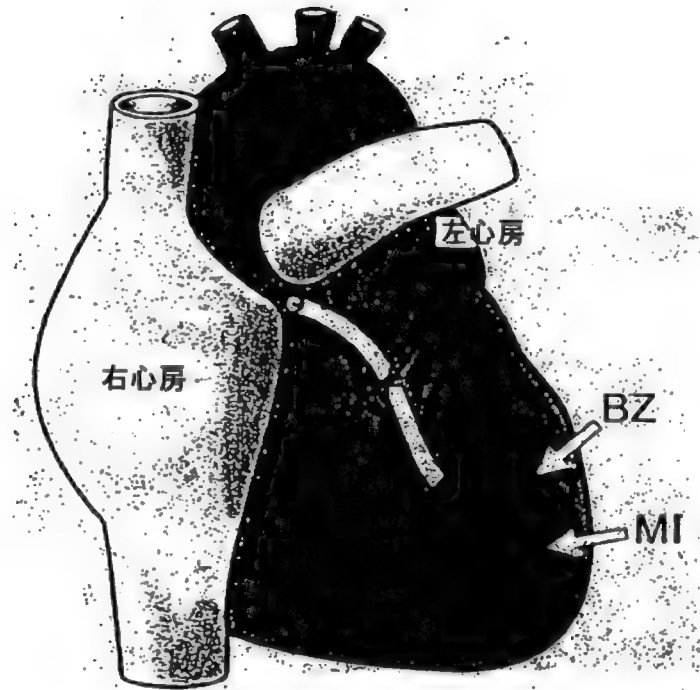


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2週間



□ □ □ □ □



□ □ □ □ □ - □ □

## 不活性CSC

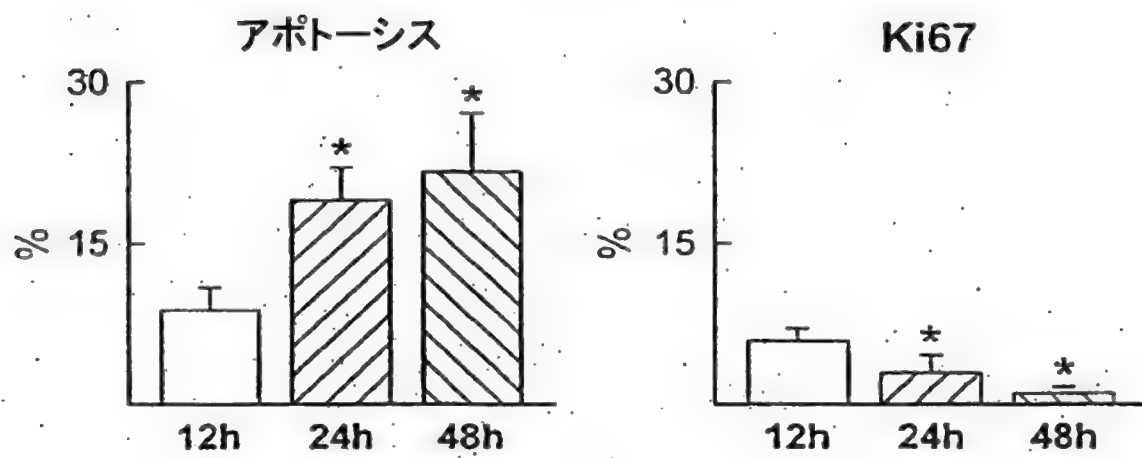


Figure 1 consists of six panels arranged in a 2x3 grid, showing fluorescence microscopy images of the developing mouse brain. The top row shows EGFP expression in the E12.5 brain, and the bottom row shows EGFP and lectin expression in the E18.5 brain. The left column shows the whole brain, the middle column shows a higher magnification of the cerebral cortex, and the right column shows a higher magnification of the hippocampus. Scale bars are provided in the bottom-left panel (16 μm) and the bottom-middle panel (42 μm).

C










□ □ □ □ □ □ □ □

60800760013



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07/04287

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 5/08 (2008.04)

USPC - 435/366

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
USPC - 435/366Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
USPC - 435/325, 384, 387, 389, 405, 406 (text search, see terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PubWEST(PGPB,USPT,EPAB,JPAB); Google/Scholar; PubMed (text search, see terms below)  
Search terms: Cardiac stem cell, hepatocyte growth factor, insulin-like growth factor, cardiomyocyte, somatic, EGF, FGF, vessel, artery, formation, regeneration, patient serum media, transferring, insulin, selenite, uridine, inosine.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0054973 A1 (ANVERSA) 20 March 2003 (20.03.2003); Claim 33, Claim 36, paras [0003], [0005], [0006], [0045], [0049], [0069], [0152], [0184], [0197]-[0199], [0274], [0276], [0307].	1-11, 13, 22, 23
Y		12, 14-21, 24-27
Y	US 2003/0105015 A1 (GILBERTSON et al.) 5 June 2003 (05.06.2003); para [0053].	12, 14-21, 24-27
Y	Insulin-Transferrin-Sodium Selenite Supplement, Datasheet [Online]. Roche Diagnostics, 2005 [retrieved on Sept. 7, 2008]. Retrieved from the Internet: <URL: http://www.roche-applied-science.com/peack-insert/1074547a.pdf>.	14-16, 19, 20, 26, 27
Y	Sellou et al. Occludin-deficient embryonic stem cells can differentiate into polarized epithelial cells bearing tight junctions. Journal of Cell Biology, 1998, vol 141, pp 397-408; (page 398, para 6).	16, 20, 27

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 September 2008 (08.09.2008)

Date of mailing of the international search report

15 SEP 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450  
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300  
PCT.OSP: 571-272-7774

26.12.2008

Form PCT/ISA/210 (second sheet) (April 2007)



(51) Int. Cl.

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43/00

□ □ □ □ 5/00 □

(81) □ □ □ AP(BW)GH GM KE, LS, MY/NZ, NA, SD, SL, SZ, TZ, UG ZM ZWY, EA(AM AZ, BY, KG KZ, MD RU, TJ, TM, EP(AT, BE, BG CH CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, I E, I S, I T, LT, LU, LV, MC, NL, PL, PT, RQ SE, SI, SK, TR), OA(BF, BJ, CF, CG, CI, CM GA, GN, GQ GW ML, MR, NE, SN, TD, TG, AE, AG AL, AM AT, AU, AZ, BA, BB, BG, BR, BW/BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, I D, I L, I N, I S, J P, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MY/MK, MY, NZ, NA, NG, N, , NQ, NZ, OM, PG, PH, PL, PT, RQ, RS, RU, SC, SD, SE, , SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

(72) □ □ □    □ □ □ □ □ □ □ □

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4C087 AA01 AA02 AA04 BB47 BB64 CA04 NA14 ZA36 ZA42 ZA45

ZB11 ZB15 ZB21